Exhibit 21

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ARBUTUS BIOPHARMA CORPORATION and GENEVANT SCIENCES GmbH, Plaintiffs, v. MODERNA, INC. and MODERNATX, INC., Defendants.	C.A. No. 22-252-MSG **CONTAINS INFORMATION DESIGNATED HIGHLY CONFIDENTIAL – OUTSIDE COUNSEL EYES ONLY BY PARTIES AND THIRD PARTIES**
MODERNA, INC. and MODERNATX, INC., Counterclaim-Plaintiffs, v. ARBUTUS BIOPHARMA CORPORATION and GENEVANT SCIENCES GmbH, Counterclaim-Defendants.	

REBUTTAL EXPERT REPORT OF ROBERT PRUD'HOMME, PH.D.

Dated: 14 February 2025

Robert K Prud'homme

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vaccines, and the [redacted]." Parsons Dep. Tr. 421:12-422:1.

235. With respect to the v2 Formulation, Dr. Mitchell alleges that "there is little data suggesting that this change [to v2 Formulation] makes any difference in Moderna's Accused Product." Mitchell Rep. ¶ 437. I disagree. As an initial matter, as Dr. Parsons testified, that he could not remember a specific time where he communicated to the FDA about data showing the v2 Formulation "[redacted]." Parsons Dep. Tr. 240:18-241:22. As Dr. Parsons testified, Moderna "[redacted]." *Id.* at 171:19-172:3.

236. Indeed, as discussed above, Moderna conducted various studies and observed that increasing the amount of PEG-DMG added [redacted]. *E.g.*, MRNA-GEN-00530699 at 701, 713; MRNA-GEN-00520077 at 077, 080; MRNA-GEN-00618958 at 965-968; MRNA-GEN-00646562 at 579.

237. Moderna also observed that, with respect to mRNA-1273 in particular, the increase of PEG to 2.5 mol% "[redacted]." MRNA-GEN-00044173 at 173; MRNA-GEN-01552012 at 013 [redacted].

238. Dr. Mitchell cites to an internal Moderna report PD-REP-0716 concerning the impact of PEG on mRNA-1273 drug product stability. Mitchell Rep. ¶¶ 439-440; MRNA-GEN-

02615528. Dr. Mitchell acknowledges that in the study, "[redacted]'" Mitchell Rep. ¶440. However, as Dr. Smith testified about this study, the data in fact supports that the PEG content has "[redacted]" Smith Dep. Tr. 277:3-279:7 ("[redacted].

239. I agree with Dr. Smith's testimony and have reproduced Table 1 and Figure 2 of the report below, showing [redacted]

Table 1: Test Article Formulation and Lipid Composition Summary						
Lot	Formulation		Lipid Composition			
	mRNA-1273 Concentration (mg/mL)	Total Lipid Concentration (mg/mL)	SM-102 (mol%)	Cholesterol (mol%)	DSPC (mol%)	PEG2000-DMG (mol%)
[redacted]						

MRNA-GEN-02615528 at 529, 530.

240. In his testimony, Dr. Smith also refers to another Moderna report from Richie Shepard, i.e. report PD-REP-0443 titled "mRNA-1273 mRNA and PEG Concentrations DOE" that I discuss in ¶ 220 above. MRNA-GEN-00967986 at 010.

241. Dr. Mitchell also cites to an interim report PD-REP-0436. Mitchell Rep. ¶441; MRNA-GEN-00736354 [redacted] Smith Dep. Tr. 268:8-270:4. Indeed, this interim report only includes one month of data. MRNA-GEN-00736354 at 354; Smith Dep. Tr. 268:8-270:4 ("One of the issues here is that in order to physically see the benefit, it takes time. So if you're studying stability of a product and you're looking at, let's say, one month, like this interim stability report, this isn't necessarily sufficient to get the full picture. Oftentimes it takes many months.").

242. Dr. Mitchell cites to a 2018 Moderna presentation and alleges that the study showed "Increasing the amount PEG-DMG spiked in provides improved protection during freeze thaw up

261. I do not see, in Dr. Mitchell's lengthy description of Moderna's research and development efforts, any other aspects that he attempts to attribute to Plaintiffs. To the extent Dr. Mitchell later identifies any additional aspects, I reserve the right to provide a further response.

2. The Molar Ratio Patents

262. During research and development for the purported inventions claimed in the Molar Ratio Patents, including the 1:57 SNALP formulation, the named inventors' narrow focus was to develop a delivery vehicle for siRNA delivery. In particular, Plaintiffs focused on siRNA delivery for therapeutics for cancer and inflammatory, metabolic, and infectious diseases. *See* MacLachlan Dep. Tr. 57:16–58:23, 65:4–15 (discussing MacLachlan's characterization of his work at Protiva and Tekmira as focused on "development of siRNA therapeutics for cancer, [] inflammatory, metabolic, and infectious disease"); Yaworski Dep. Ex. 4 (GENV-00888812) at 5 (identifying design of specific SNALP formulations for "different cell and tissue targets (e.g., oncology)" as one of two goals of the named inventors' reformulation efforts). The reformulation efforts captured in the Molar Ratio Patents did *not* involve work with mRNA or vaccines.

263. This narrow focus is reflected in the Molar Ratio Patents' specification, which discloses only examples relating to siRNA encapsulation. *See, e.g.*, '069 Patent at Examples 1–11 (68:5–86:18). Additionally, the specification emphasized the goal of the invention as finding a lipid delivery vehicle for siRNA to treat cancer and atherosclerosis. '069 Patent at 2:55–60 ("[T]here remains a strong need in the art for novel and more efficient methods and compositions for introducing nucleic acids such as siRNA into cells. In addition, there is a need in the art for methods of downregulating the expression of genes of interest to treat or prevent diseases and disorders such as cancer and atherosclerosis."). Because the siRNA was to be delivered intravenously to reach distal target tissues, the patent specification emphasizes extended serum stability. '069 Patent at 5:58–61 ("Additionally, the SNALP of the invention are stable in

circulation, e.g., resistant to degradation by nucleases in serum, and are substantially non-toxic to mammals such as humans."), 6:13–19 ("For instance, the "1:57 SNALP" and "1:62 SNALP" formulations described herein are exemplary formulations of the present invention that are particularly advantageous because they provide improved efficacy and tolerability in vivo, are serum-stable, are substantially non-toxic, are capable of accessing extravascular sites, and are capable of reaching target cell populations.").

264. The named inventors' work leading up to the first application for the Molar Ratio Patents had absolutely no relation to mRNA LNPs. Prior to 2013, their work was focused on siRNA delivery. Jeffs Dep. Tr. 142:25–143:18 ("Q. … Can you recall working on any other nucleic acids other than siRNA [in 2008, when provisional application 61/045,228 was filed]? … A. I can't recall specifically."); Lam Dep. Tr. 88:4–10 ("Q. In connection with the experiments that are reported in the '069 patent, … you worked with siRNA; is that right? A. So the experiment specifically that is outlined in example 2, that is sRNA [sic], but we have made at least a 2:40 composition with plasmid DNA prior to this experiment."); GENV-00304863 at 864 ("While Tekmira's focus has chiefly been delivery of small interfering RNAs (siRNAs) in order to effect gene silencing, in 2013 we turned our attention to delivery of messenger RNA (mRNA) transcripts."). In April 2008, Plaintiffs and the named inventors still had not applied the claimed lipid molar ratios to mRNA encapsulation, nor had they developed or investigated any mRNA LNP formulations. Genevant 11th Supp. Resp. to Moderna 1st Set of ROGs at 172 (Plaintiffs "first encapsulated mRNA in an LNP composition in or around November 2009"); MacLachlan Dep. Tr. 134:11–135:7 ("[P]rior to 2008, there was no research, development, and use of mRNA with the lipid particles comprising the lipid ratios of the asserted claims of the molar ratio patents."); Jeffs Dep. Tr. 154:9–17 ("Q. By 2008, when the application that led to the '069 was filed, can you

b. No Infringement of the ≥50 mol% Cationic Lipid Range Limitations Under the Doctrine of Equivalents

455. I disagree with Dr. Mitchell's opinion that Moderna's SPIKEVAX® v1 Formulation infringes the following claims under the doctrine of equivalents (and the asserted claims that depend from them): '069 patent, claim 1; '359 patent, claims 1, 7; '668 patent, claims 1, 8; '435 patent, claim 1. *See* Mitchell Rep. ¶ 654, n. 132.

456. For the reasons explained in Sections X.D.1 and X.D.3.a, under Plaintiffs' view of the claims and Plaintiffs' new infringement theory that focuses on the lipid content of individual lipid particles, the Certificates of Analysis do not provide evidence of the lipid content of any individual particle, and do not show that any individual particles meet Plaintiffs' hypothetical claims.

i. Dr. Mitchell's DOE Analysis

457. Dr. Mitchell bases his doctrine of equivalents analysis on "statements made by Moderna's employees, and representations Moderna has made to the FDA." Mitchell Rep. ¶ 655. But the FDA's concepts of equivalents, comparability, and bioequivalence of the overall product are different than the inquiry of whether an individual element in a product infringes a claim limitation under the doctrine of equivalents. *See* Godshalk Rep. §§ V, VI. Additionally, rather than comparing the claimed element to the missing element in Moderna's product, Dr. Mitchell compares three versions of Moderna's product. Moreover, changes to the lipid molar ratio percentages can impact various properties of the LNP. *See, e.g.,* MRNA-GEN-00554883 [redacted] MRNA-GEN-00547814 [redacted]; MRNA-GEN-00533651 [redacted]

(A) Function (≥50 mol% Cationic Lipid Range Limitations)

458. Dr. Mitchell conflates equivalence of the function of the cationic lipid broadly with the function of the specific claimed molar percentages of the cationic lipid. I disagree with Dr. Mitchell's conclusion that "[t]he function of the SM-102 cationic lipid and its mol % concentration in drug product lots of the Accused Product, including within lots formulated with the PVU, v1, and v2 Formulations, is substantially the same as the cationic lipid and its mol % in the claimed invention." Mitchell Rep. ¶¶ 656-657.

459. Dr. Mitchell's conclusion relies on Moderna's statements to the FDA that [redacted] Mitchell Rep. ¶ 657 citing MRNA-GEN-00988461 at -468. Dr. Mitchell opines that the function of the concentration of SM-102 in the v1 and v2 Formulation is equivalent to that of the claimed ⩾50 mol % cationic lipid range because Moderna's description, which would apply to any LNP encapsulating mRNA, "remained constant throughout Moderna's regulatory submissions, notwithstanding the change in the target cationic lipid mol % in the v1 and v2 formulations." Mitchell Rep. ¶ 657. This fails to address the impacts of changing the cationic lipid mol % concentration, discussed below at Section X.D.3.b.ii. And again, the FDA's concepts of equivalents, comparability, and bioequivalence are different than the theory of patent infringement by the doctrine of equivalents. *See* Godshalk Rep. §§ V, VI.

460. Dr. Mitchell fails to compare SM-102 at 48.5 mol % to any of the embodiments or examples of cationic lipids and/or formulations disclosed in the Molar Ratio Patents. Dr. Mitchell

also ignores that the Molar Ratio Patents define the function of cationic lipids as "forming lipid particles with increased membrane fluidity." '069 Patent at 12:53-57.

(B) Way (≥50 mol% Cationic Lipid Range Limitations)

461. Dr. Mitchell's finding that "the SM-102 cationic lipid and its mol % concentration in drug product lots of the Accused Product, including within lots formulated with the PVU, v1, and v2 Formulations, [] perform[s] substantially the same function of the cationic lipid of the Asserted Claims, including its recited mol %, in substantially the same way" is conclusory. Mitchell Rep. ¶ 659. Dr. Mitchell articulates only that "[t]he way in which the SM-102 lipids of the drug product achieve their function is through their structure, chemical composition, and concentration, which enables the lipids to carry a positive charge in acidic conditions and subsequently helps to drive interactions, including with the nucleic acid during encapsulation" and that "the SM-102 lipids in all lots of Moderna's COVID-19 vaccine drug product, regardless of the target or measured mol % of SM-102 in that lot, are the same structure and possess the same structural features." Mitchell Rep. ¶¶ 659-660.

462. Even if he is right that the function of the cationic lipid is to "provide a positive electrostatic charge that subsequently interacts with the negative charge of the nucleic acid to facilitate encapsulation of the nucleic acid," [redacted] *See* Section VIII.A.3.a.

463. Further, Dr. Mitchell ignores that unlike the lipids identified by the Molar Ratio Patents as being "particularly useful for forming lipid particles with increased membrane fluidity," '069 Patent at 12:53-57, SM-102 does not comprise alkyl chains with multiple sites of unsaturation. Indeed, SM-102 does not contain any unsaturation. *See* Section X.D.3.b.ii(B) below.

(C) Result (≥50 mol% Cationic Lipid Range Limitations)

464. Dr. Mitchell's finding that "the SM-102 cationic lipid and its mol % concentration in drug product lots of the Accused Product, including within lots formulated with the PVU, v1, and v2 Formulations achieve substantially the same result as the cationic lipid and its mol % in the claimed invention" likewise relies on the overbroad premise that "the result of the cationic lipid limitation, including its recited mol % in the claims, in the context of the invention as a whole, is the effective and efficient intracellular delivery of nucleic acid." Mitchell Rep. ¶ 661. Again, this would apply broadly to LNPs encapsulating nucleic acid. Dr. Mitchell opines that "Moderna's COVID-19 vaccine drug product, whether formulated with the PVU, v1, or v2 Formulations, including drug product formulations with reported cationic lipid content values of 45 to 50 mol % cationic lipid, achieve substantially the same result, including with respect to efficacy (immunogenicity), safety, and stability compared to formulations using 50 mol % cationic lipid . . . ." Mitchell Rep. ¶ 661. But in support of his opinion, Dr. Mitchell conflates clinical equivalency and chemical equivalency. For example, Dr. Mitchell cites Don Parsons' testimony: [redacted]

Mitchell Rep. ¶ 661 citing Parsons 6/7/2024 Dep. Tr. at 202:17-203:4 (emphasis added). And Dr. Mitchell cites an e-mail chain discussing [redacted] but takes it out of context and does not account for e-mails later in the chain that explain that [redacted] Mitchell Rep. ¶ 662 citing MRNA-GEN-00601091.

465. Dr. Mitchell also fails to address evidence showing, for example, that [redacted] MRNA-GEN-00539393 at MRNA-GEN-00539397; *see also* MRNA-GEN-00533651 at MRNA-GEN-00533662 [redacted] MRNA-GEN-00533651 at MRNA-GEN-00533664 [redacted].

466. Moreover, Dr. Mitchell ignores the results articulated in the Molar Ratio Patents including that efficient silencing of protein expression was found based on intravenous delivery, which was surprising with the higher levels of cationic lipid. *See, e.g.,* '069 Patent at 5:44-6:19.

(D) Substantial Differences (≥50 mol% Cationic Lipid Range Limitations).

467. I disagree with Dr. Mitchell's opinion that "the cationic lipid content of each lot of Moderna's COVID-19 drug product, including lots formulated with the PVU, v1, and v2 Formulations, are insubstantially different both from one another and insubstantially different from the claimed cationic lipid mol % limitation." Mitchell Rep. ¶ 667. Dr. Mitchell states that "Moderna's express goal when changing its formulation of various vaccine programs in the 2018-2019 timeframe and again in 2020 for the COVID-19 vaccine drug product was to create a product that was insubstantially different from its formulations with 50 mol % cationic lipid in order to avoid the need to conduct additional clinical trials." Mitchell Rep. ¶ 669. But the FDA's concepts of equivalents, comparability, and bioequivalence are different than the theory of patent infringement by the doctrine of equivalents. *See* Godshalk Rep. §§ V, VI. Moreover, Dr. Mitchell improperly bases his analysis on differences between Moderna's formulations (e.g., comparing PVU to v1) rather than comparing each formulation to the asserted claims (e.g., comparing the cationic lipid at ≥50 mol % in the asserted claims to the 48 mol % SM-102 in Moderna's v1).

(E) Hypothetical Claims (≥50 mol% Cationic Lipid Range Limitations).

468. I understand that the doctrine of equivalents analysis may be conducted by constructing a "hypothetical claim" and assessing whether the Accused Product would literally infringe that claim. Dr. Mitchell opines that a "potential 'hypothetical claim' would recite a nucleic acid-lipid particle where the lower limit on the amount of cationic lipid is 45 mol %, rather than 50 mol %." Mitchell Rep. ¶ 679. For the reasons explained above, I disagree with Dr. Mitchell's predicate statement that [redacted] and with his findings based on that false premise. Mitchell Rep. ¶ 679.

469. Additionally, for the reasons explained in Sections X.D.1 and X.D.3.a, under Plaintiffs' view of the claims and Plaintiffs' new infringement theory that focuses on the lipid content of individual lipid particles, the Certificates of Analysis do not provide evidence of the lipid content of any individual particle, and do not show that any individual particles meet Plaintiffs' and Dr. Mitchell's hypothetical claims.

ii. My Function-Way-Result Analysis

470. In my opinion, the 48.5 mol % SM-102 cationic lipid in Moderna's SPIKEVAX® v1 Formulation has a different function, way, and result, and is substantially different from, the claimed ≥50 mol % cationic lipid ranges in the Molar Ratio Patents. Additionally, although I refer below to Moderna's target v1 Formulation with 48.5 mol % SM-102 cationic lipid, Dr. Mitchell also contends that the claim extends to 45 mol % cationic lipid under the doctrine of equivalents, which I considered as part of my analysis.

(A) Function (≥50 mol% Cationic Lipid Range Limitations)

471. In my opinion, the ≥50 mol % cationic lipids claimed in the Molar Ratio Patents serve different functions as compared to the 48.5 mol % SM-102 in the v1 Formulation. At a high level, the higher level (i.e. ≥50 mol %) of cationic lipid claimed in the Molar Ratio Patents forms lipid particles with increased membrane fluidity to efficiently deliver siRNA to distal sites (e.g. tumor). Meanwhile, the 48.5 mol % SM-102 in the v1 Formulation [redacted]

(1) The Function of the ≥50 mol% Cationic Lipid Range Limitations in the Asserted Claims

472. The specification of the Molar Ratio Patents explains that there are distinct benefits of using 50 mol % or more of a cationic lipid and that these distinct benefits were material to the patentability of the Molar Ratio Patents. Specifically, the specification explains: "***The present invention is based, in part, upon the surprising discovery that lipid particles comprising from about 50 mol % to about 85 mol % of a cationic lipid***, from about 13 mol % to about 49.5 mol % of a non-cationic lipid, and from about 0.5 mol % to about 2 mol % of a lipid conjugate ***provide advantages when used for the in vitro or in vivo delivery of an active agent, such as a therapeutic nucleic acid (e.g., an interfering RNA).***" '378 Patent at 6:6-13 (emphasis added).

473. Regarding the function of the ≥50 mol% cationic lipid in the Asserted Claims, the specification of the Molar Ratio Patents explains: "It has surprisingly been found that cationic lipids comprising alkyl chains with multiple sites of unsaturation, e.g., at least two or three sites of unsaturation, are particularly useful for forming lipid particles with increased membrane fluidity." '069 Patent at 12:53-57.

474. The prosecution history of the Molar Ratio Patents further supports the distinct benefits of 50 mol % or more of a cationic lipid in an LNP. During prosecution of the '069 patent, the examiner explained: "It is clear from the specification that the present invention is based, in

part, on the surprising discovery that 1:57 SNALP formulations provide new and unexpected results when used for the *in vitro* or *in vivo* delivery of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA). More particularly, Applicants have found that SNALP formulations having **increased** amounts of cationic lipid, *e.g.*, one or more cationic lipids comprising from about 50 mol % to about 65 mol % of the total lipid present in the particle, provide ***unexpectedly superior advantages*** when used for the *in vitro* or *in vivo* delivery of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA)." '069 File History Jan. 31, 2011 at 9.

475. Ultimately, the examiner explained in the Notice of Allowance that the narrowed ranges of molar ratios was the sole basis for allowance: "The prior art of record is considered pertinent to applicant's disclosure. US 6,815,432, cited on an IDS discloses lipid formulations but does not appear to disclose the ranges for each of the lipids recited in the instant claims." *See* '069 (Notice of Allowance) at 6. In other words, the Examiner accepted Applicant's arguments of unexpected results, which overcame the prior art rejections.

476. Moreover, Arbutus repeated this reliance on unexpected results during the IPR: "The '435 patent is directed to the surprising discovery that nucleic acid-lipid particles with ***high levels of cationic lipids*** and low levels of conjugated lipids exhibit favorable *in vivo* transfection efficiencies, as well as 'improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described.'" '435 Appeal, D.I. 67) at 19 (emphasis added). Arbutus further explained that this "surprising discovery" solved a long-felt need material to patentability: "The nucleic acid-lipid particle formulations of the '435 patent solved a long-felt need for compositions that could safely and effectively deliver nucleic acids to target cells of patients. Skilled artisans were skeptical

that compositions ***having high levels of cationic lipid (i.e., 50 mol % to 85 mol %)*** and low levels of conjugated lipid (i.e., 0.5 mol % to 2 mol %) would be effective, let alone well-tolerated when administered *in vivo*. The combination of ***effectiveness*** and low toxicity that characterizes the claimed compositions surprised many in the field, and finally solved the delivery problem that hindered the field for decades." '435 IPR, PO Response at 2 (emphasis added). Additionally, Arbutus distinguished their alleged invention of "a nucleic acid-lipid particle comprised of relatively high levels of cationic lipids and low levels of conjugated lipids" from the prior art, which it argued taught that the cationic lipid components of lipid particles "should be minimized": "The claimed invention is a nucleic acid-lipid particle comprised of relatively high levels of cationic lipids and low levels of conjugated lipids. This combination was counterintuitive to the then-existing state of the art, as cationic lipids were known to be cytotoxic, systemically toxic, to elicit an adverse complement-mediated immune response, and to cause particle aggregation that resulted in rapid clearance. *E.g.,* EX1007, 745 ("Minimizing the amount of cationic lipid is desirable . . . fewer, more highly charged molecules should mean a smaller metabolic effort. . .") EX1009, 5 ("the cationic lipid contributes significantly to the toxicity observed."); EX2016, 42 ("I wouldn't want anyone injecting cationic lipids into my bloodstream."). The prior art taught that the cationic lipid component of lipid particles should be minimized, regardless of whether used for *in vitro* or *in vivo* purposes. EX20231, ¶¶80-88." '069 IPR, PO Response at 29.

477. Based on Arbutus's statements in the specification of the Molar Ratio Patents and the intrinsic record (including the file history and the *Inter Partes* Reviews), the function of the claimed higher levels (i.e. ≥50 mol %) cationic lipid ranges is to safely and effectively deliver a therapeutic nucleic acid (*e.g.,* an interfering RNA) to distal target cells.

(2) The Function of 48.5 mol% SM-102 in the v1 Formulation

478. The 48.5 mol % of SM-102 in Moderna' COVID-19 Vaccine functions by [redacted]. In particular, Moderna's lower concentration of its proprietary SM-102 cationic lipid achieves [redacted] *See* Section VIII.A.5. For the reasons explained above, 48.5 mol % SM-102 in the v1 Formulation functions differently than the ≥50 mol % cationic lipid claimed in the Molar Ratio Patents.

(B) Way (≥50 mol% Cationic Lipid Range Limitations)

479. In my opinion, the 50 mol % cationic lipid claimed in the Molar Ratio Patents function in a different way to the 48.5 mol % SM-102 in the v1 Formulation. By being present at higher levels, the ≥50 mol % cationic lipids claimed in the Molar Ratio Patents functions to increase membrane fluidity due to alkyl chains with multiple sites of unsaturation. Meanwhile, by being present at lower levels, the 48.5 mol % SM-102 in the v1 Formulation [redacted].

(1) The Way of ≥50 mol% Cationic Lipid Range Limitations in the Asserted Claims

480. The Molar Ratio Patents define "cationic lipid" as follows:

> The term 'cationic lipid' refers to any of a number of lipid species that carry a net positive charge at a selected pH. Such as physiological pH (e.g., pH of about 7.0). It has been surprisingly found that cationic lipids ***comprising alkyl chains with multiple sites of unsaturation, e.g., at least two or three sites of unsaturation, are particularly useful for forming lipid particles with increased membrane fluidity***. A number of cationic lipids and related analogs, which are also useful in the present invention, have been described in U.S. Patent Publication Nos. 20060083780 and 20060240554; U.S. Pat. Nos. 5,208,036; 5,264,618: 5,279,833; 5,283,185; 5,753,613; and 5,785,992; and PCT Publication No. WO96/10390, the disclosures of which are herein incorporated by reference in their entirety for all purposes. Non-limiting examples of cationic lipids are described in detail herein. In some cases, the cationic lipids comprise a protonatable tertiary amine (e.g., pH titratable) head group, C18 alkyl chains, ether linkages between the head group and alkyl chains,

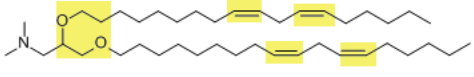
> and 0 to 3 double bonds. Such lipids include, e.g., DSDMA, DLinDMA, DLenDMA, and DODMA.

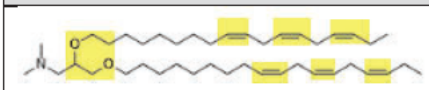
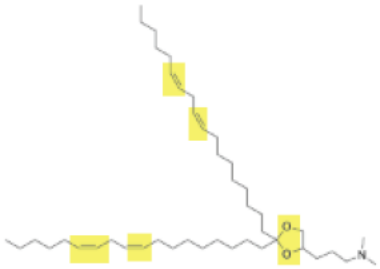
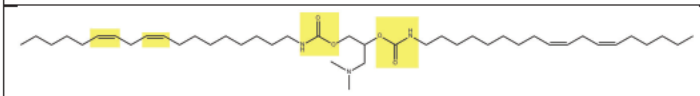
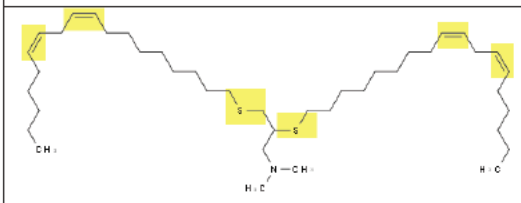
'069 Patent at 12:51-13:3 (emphasis added). Specifically, the Molar Ratio Patents explain that "[i]t has been surprisingly found that cationic lipids comprising alkyl chains with multiple sites of unsaturation, e.g., at least two or three sites of unsaturation, are particularly useful for forming lipid particles with increased membrane fluidity." '069 Patent at 12:53-57. In other words, the Molar Ratio Patents explain that "cationic lipids comprising alkyl chains with multiple sites of unsaturation" help to fuse the target cell to allow delivery of siRNA, thus identifying the way in which the 50 mol % cationic lipid functions.

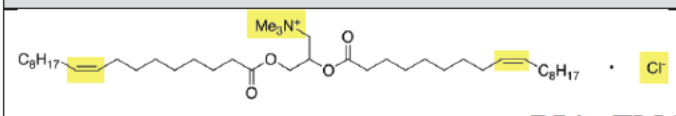
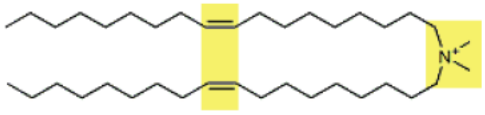
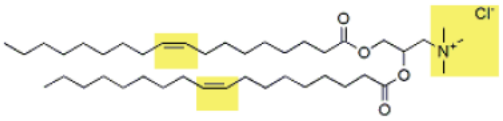
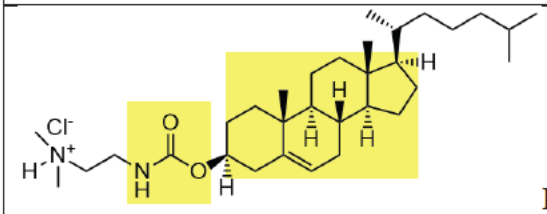
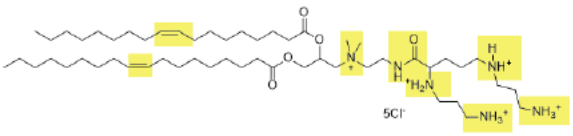
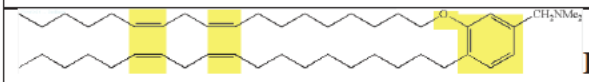
(2) The Way of 48.5 mol% SM-102 in the V1 Formulation

481. The ≥50 mol % cationic lipids disclosed in Molar Ratio Patents, such as DLinDMA, function in a different way from the 48.5 mol % SM-102 in the v1 Formulation. For example, unlike the lipids identified by the Molar Ratio Patents as being "particularly useful for forming lipid particles with increased membrane fluidity," '069 Patent at 12:53-57, SM-102 does not comprise alkyl chains with multiple sites of unsaturation. Indeed, SM-102 does not contain any unsaturation. [redacted].

482. There are other material differences between SM-102 and the specific cationic lipids disclosed in the Molar Ratio Patents. Examples of chemical features that are found in cationic lipids disclosed in the Molar Ratio Patents but not present in SM-102:

Cationic lipids disclosed in Molar Ratio Patents	Chemical features NOT present in SM-102
 **DLinDMA**	**Ethers; alkenes**

Cationic lipids disclosed in Molar Ratio Patents	Chemical features NOT present in SM-102
 DLenDMA  DODMA  DLin-KC2-DMA  DLin-KC3-DMA  DLin-KC4-DMA	
 DLin-C-DAP	Carbamoyl esters; alkenes
 DLin-S-DMA	Thioethers; alkenes

Cationic lipids disclosed in Molar Ratio Patents	Chemical features NOT present in SM-102
 **DLin-TMA.Cl**  **DODAC**  **DOTMA**	**Quaternary ammonium salt; alkenes**
 **DC-Chol**	**Carbamoyl esters; sterol nucleus**
 **DOSPA**	**Quaternary ammonium salt; polyamines; alkenes; amide**
 **DMLBA**	**Aryl ether, alkenes**

483. The CO-O functions in SM-102 are esters and not ethers, and a POSA would understand that esters and ethers are not chemically equivalent. The esters are the feature of the SM-102 that make it biodegradable and suitable for IM dosing, which is not taught by the Molar Ratio Patents, which focuses on alkyl chains with multiple sites of unsaturation. *See* Hassett 2019 at 2 ("The ionizable lipids screened here all contain a tertiary amine with ester-containing lipid tails to enable rapid *in vivo* metabolism."). Accordingly, the underlying mechanism of action for SM-102 is not equivalent to the mechanism for the cationic lipids disclosed in the Molar Ratio

Patents. In fact, the ester linkages in the hydrophobic tails of Moderna's SM-102 lipid increase the rate of degradation of the lipid in the cytosol, and decrease the toxicity and immunogenicity of the LNP formulation.

484. Although MC3 is not disclosed in the Molar Ratio Patents (*see* Section IX.B.2) the evidence shows that [redacted] MC3. *E.g.*, Benenato Dep. Tr. at 64:14-65:1, 72:5-11; MRNA-GEN-00508894 at 926-927; *see also* Benenato Dep. Ex. 8, MRNA-GEN-01062618, MRNA-GEN-00036907, MRNA-GEN-01625914, MRNA-GEN-00769265. Additionally, Genevant scientists themselves, including Kieu Lam and Lorne Palmer, named inventors to the Molar Ratio Patents, acknowledged that SM-102 and MC3 are considerably more potent than DLinDMA. *E.g.*, GENV-00951182 at 182, 185.

485. Further, I note that the Molar Ratio Patents state "[i]t has been surprisingly found that cationic lipids comprising alkyl chains with multiple sites of unsaturation, e.g., at least two or three sites of unsaturation, are particularly useful for forming lipid particles with increased membrane fluidity." '069 patent at 12:53-58. In contrast, Moderna's SM-102 lipid has no unsaturation. A POSA would understand the role of unsaturation in the classes of lipids described in the Molar Ratio Patents to be the prevention of the crystallization of the lipid tails, thus "increase[ing] membrane fluidity."[41] In contrast to unsaturation to maintain membrane fluidity, Moderna's SM-102 has branched lipid tails conjugated from ester-linked precursors. This branching prevents crystallization and enhances fluidity, but it is the steric interference that increases fluidity, rather than unsaturation.

[41] Membrane fluidity describes the mobility of the outer membrane surface of an LNP. The fluidity is determined not only by the type of lipid tail of the ionizable lipid, but also by the amount of cholesterol and neutral lipid that is incorporated into the LNP, which partitions to the surface.

486. Further confirming that the "way" is different, Plaintiffs' documents[42] confirm that using lower levels of cationic lipid than claimed led to unfavorable results, whereas those same negative attributes are not applicable to the 48.5 mol % SM-102 used in the v1 Formulation. For example, the inventors found that lower levels of cationic lipid have a negative impact on activity, whereas higher amounts such as 57 mol % led to greater activity. GENV-00126198-348 at GENV-00126202, at 208; GENV-00063772, 73 at 78 (similar findings); GENV-00058026 at 032 (table Dr. Mitchell identified as underlying the Molar Ratio Patents, Table 2, shows lower cationic lipids performed poorer (with a higher IC-50) than Sample 9, the 1:57 formulation), at 034 (same, with respect to poor stability for lower cationic molar percentages, e.g. 53 mol %, compared to 57 mol % in the 1:57 embodiment), at 039 ("increasing the concentration of DLinDMA in formulation had strong positive effect on activity"). In fact, the inventors even noted that reducing cationic lipid DLinDMA in conjunction with an increase in PEG led to a strong negative effect. GENV-00126202, 214 (***"when DLinDMA (-)*** [i.e. reduced] and DPPC (+) - ***increasing PEG had a negative effect***"); *see also* GENV-00057731 (describing findings that high cationic lipid showed more rapid blood clearance, compared to low cationic lipid formulations which had slower blood clearance); GENV-00109171 ("the most potent formulation contains the highest mol% cationic lipid; reducing cationic lipid content by increasing cholesterol, DPPC, and PEG-C-DMA caused loss of activity"), at 82 ("reducing PEG-lipid concentration further may benefit activity"). During development of Moderna's COVID-19 Vaccine, by comparison, [redacted]

[redacted]

[redacted]

[42] To determine the function-way-result of the claim limitation, I considered the specification and the file history. I refer to Plaintiffs' documents here as they are consistent with my opinions based on the specification and file history.

[redacted], which confirms that Moderna's cationic lipid at 48.5 mol % is acting in a different way to the cationic lipid at ≥50 mol % of the asserted claims. *See* Section VIII.A.4; *see also, e.g.* Parsons Dep. Ex. 40 at MRNA-GEN-00533662 [redacted].

(C) Result (≥50 mol% Cationic Lipid Range Limitations)

487. ≥50 mol % cationic lipid in the Asserted Claims of the Molar Ratio Patents achieve different results than 48.5 mol % cationic lipid. At a high level, the ≥50 mol % cationic lipids claimed in the Molar Ratio Patents efficiently delivers the siRNA payload to cells (e.g., tumor or distal targets such as the liver). Meanwhile, the 48.5 mol % SM-102 in the v1 Formulation achieves the balance between efficient protein expression and biodegradability (lipid is cleared quickly from the injection site) for intramuscular vaccine delivery, which as described above for the "way" was a result that the inventors were unable to achieve with the disclosed compositions and cationic lipids at 50mol% disclosed in the Molar Ratio Patents

(1) The Result of ≥50 mol% Cationic Lipid Range Limitations in the Asserted Claims

488. The specification of the Molar Ratio Patents explains that there are distinct benefits of 50 mol % or more cationic lipid and that these distinct benefits were material to the patentability of the Molar Ratio Patents. Specifically, the specification explains:

> ***The present invention is based, in part, upon the surprising discovery that lipid particles comprising from about 50 mol % to about 85 mol % of a cationic lipid***, from about 13 mol % to about 49.5 mol % of a non-cationic lipid, and from about 0.5 mol % to about 2 mol % of a lipid conjugate ***provide advantages when used for the in vitro or in vivo delivery of an active agent, such as a therapeutic nucleic acid (e.g., an interfering RNA).*** In particular, as illustrated by the Examples herein, the present invention ***provides stable nucleic acid-lipid particles (SNALP) that advantageously impart increased activity of the encapsulated nucleic acid*** (e.g., an interfering RNA such as siRNA) and ***improved tolerability of the formulations in vivo***, resulting in a ***significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described***. Additionally, the

> SNALP of the invention are stable in circulation, e.g., resistant to degradation by nucleases in serum, and are substantially non-toxic to mammals such as humans. As a non-limiting example, FIG. 3 of Example 4 shows that one SNALP embodiment of the invention ("1:57SNALP) was more than 10 times as efficacious as compared to a nucleic acid-lipid particle previously described ("2:30 SNALP) in mediating target gene silencing at a 10-fold lower dose. Similarly, FIG. 2 of Example 3 shows that the "1:57 SNALP" formulation was substantially more effective at silencing the expression of a target gene as compared to nucleic acid-lipid particles previously described ("2:40 SNALP).
>
> In certain embodiments, the present invention provides improved compositions for the delivery of interfering RNA such as siRNA molecules. In particular, the Examples herein illustrate that the improved lipid particle formulations of the invention are highly effective in downregulating the mRNA and/or protein levels of target genes. Furthermore, the Examples herein illustrate that ***the presence of certain molar ratios of lipid components results in improved or enhanced activity of these lipid particle formulations of the present invention***. For instance, the "1:57 SNALP and "1:62 SNALP formulations described herein are exemplary formulations of the present invention that are particularly advantageous because they ***provide improved efficacy and tolerability in vivo***, are serum-stable, are substantially non-toxic, are capable of accessing extravascular sites, and are capable of reaching target cell populations.

'069 Patent at 5:44-6:19. (emphasis added). This passage of the specification confirms that the result of the use of higher levels of cationic lipid in the asserted claims is increased activity of the encapsulated siRNA, which are delivered intravenously to distal sites.

489. As explained above, the prosecution history of the Molar Ratio Patents further supports the distinct benefits of a lipid particle comprising 50 mol % or more cationic lipid. During prosecution of the '069 patent, the examiner explained: "It is clear from the specification that the present invention is based, in part, on the surprising discovery that 1:57 SNALP formulations provide new and unexpected results when used for the *in vitro* or *in vivo* delivery of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA). More particularly, Applicants have found that SNALP formulations having **increased** amounts of cationic lipid, *e.g.*, one or more cationic lipids comprising from about 50 mol % to about 65 mol % of the total lipid present in the particle, provide ***unexpectedly superior advantages*** when used for the *in vitro* or *in vivo* delivery

of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA)." '069 File History Jan. 31, 2011 at 9.

490. Ultimately, the examiner explained in the Notice of Allowance that the narrowed ranges of molar ratios was the sole basis for allowance: "The prior art of record is considered pertinent to applicant's disclosure. US 6,815,432, cited on an IDS discloses lipid formulations but does not appear to disclose the ranges for each of the lipids recited in the instant claims." *See* '069 Notice of Allowance at 6.

491. Moreover, Arbutus repeated this disclaimer and reliance on unexpected results during IPR: "The '435 patent is directed to the surprising discovery that nucleic acid-lipid particles with ***high levels of cationic lipids*** and low levels of conjugated lipids exhibit favorable ***in vivo transfection efficiencies***, as well as 'improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described.'" '435 Appeal, D.I. 67 at 19 (emphasis added). Arbutus further explained that this "surprising discovery" solved a long-felt need material to patentability: "The nucleic acid-lipid particle formulations of the '435 patent solved a long-felt need for compositions that could safely and effectively deliver nucleic acids to target cells of patients. Skilled artisans were skeptical that compositions having high levels of cationic lipid (i.e., 50 mol % to 85 mol %) and low levels of conjugated lipid (i.e., 0.5 mol % to 2 mol %) would be effective, let alone well-tolerated when administered *in vivo*. The combination of effectiveness and low toxicity that characterizes the claimed compositions surprised many in the field, and finally solved the delivery problem that hindered the field for decades." '435 IPR, PO Response at 2 (emphasis added). Additionally, Arbutus distinguished their alleged invention of "a nucleic acid-lipid particle comprised of relatively high levels of cationic lipids and low levels of conjugated lipids" from the

prior art, which it argued taught that the cationic lipid components of lipid particles "should be minimized": "The claimed invention is a nucleic acid-lipid particle comprised of relatively high levels of cationic lipids and low levels of conjugated lipids. This combination was counterintuitive to the then-existing state of the art, as cationic lipids were known to be cytotoxic, systemically toxic, to elicit an adverse complement-mediated immune response, and to cause particle aggregation that resulted in rapid clearance. *E.g.,* EX1007, 745 ("Minimizing the amount of cationic lipid is desirable . . . fewer, more highly charged molecules should mean a smaller metabolic effort. . .") EX1009, 5 ("the cationic lipid contributes significantly to the toxicity observed."); EX2016, 42 ("I wouldn't want anyone injecting cationic lipids into my bloodstream."). The prior art taught that the cationic lipid component of lipid particles should be minimized, regardless of whether used for *in vitro* or *in vivo* purposes. EX20231, ¶¶80-88." '069 IPR, PO Response at 29. This is consistent with my opinion that that nucleic acid-lipid particles comprising [≥50] mol% cationic lipid achieve different results than nucleic-acid lipid particles comprising <50 mol % cationic lipid.

(2) The Result of 48.5 mol% SM-102 in the v1 Formulation

492. The use of ≥50 mol % cationic lipids in the Asserted Claims achieve a different result as compared to 48.5 mol% SM-102 in the v1 Formulation.

493. For background, Dr. Kerry Benenato, a former Moderna scientist, invented a new cationic lipid called SM-102 for mRNA delivery that was ultimately used in Moderna's COVID-19 Vaccine. Benenato Dep. Tr. 74:7-76:14. Early in the evaluation of LNPs as a delivery system for mRNA vaccines, Moderna used MC3 as an ionizable lipid to deliver mRNA vaccines. Hassett 2019 at 6 ("MC3 formulated mRNA was the worst tolerated lipid tested whereas SM-102 was the best tolerated lipid tested."). [redacted]

[redacted]. MRNA-GEN-00018601 at -603. [redacted], [redacted]. MRNA-GEN-00480514 at Figure 8. MRNA-GEN00018601 at -603.

494. SM-102 was also selected as the amino lipid for IM delivery of LNPs for reasons including because it was the most potent lipid out of a panel of at least 30 ionizable lipids that were screened for expression and vaccine potency for the intramuscular (IM) route of administration in rodents. MRNA-GEN-00988589 at -591; MRNA-GEN-00480514; MRNA-GEN00018601 at -603; Hassett 2019 at 2; *see also* MRNA-GEN-00480514 at -514 ("1. Increases expression 3x over MC3 LNPs in NHP 2. Equal immunogenicity as MC3 LNPs in NHP 3. Minimal site of injection reaction observed in NHP 4. Lowest pathology scores in the non-GLP rat tolerability study 5. Able to be formulated using a micro-tee 6. Stable up to 1 month stored in 20mM tris 8% sucrose at 0.2 mg/ml").

495. Moderna reported SM-102 having increased expression in NHPs and rodents as compared to MC3. MRNA-GEN-00480514 at -514, Figure 2 ("SM-102 and SM-107 were shown to exhibit 4-6x MC3 expression in mice."); MRNA-GEN-00480514 at -514, Figure 4 ("SM-102 had 3x the expression of MC3 LNPs."). Moderna also reported SM-102 as having increased immunogenicity in mice and similar immunogenicity as NHPs compared to MC3. MRNA-GEN-00480514 at -514, Figure 3 and 5 ("SM-102 and SM151 produced the highest titers in mice and SM-102, SM-140 and SM-151 LNPs had titers similar to MC3 in cynomolgus macaques."); 4 ("In NHPs, while three out of the five selected lipids yielded comparable expression to MC3-based LNPs, SM-102 lipid and Lipid M showed significantly more expression over time than MC3. For

SM-102, the maximum antibody concentration measured 24 hours post injection was three times the antibody concentration measured with MC3 formulated material.").

496. In addition to SM-102 having higher expression and similar immunogenicity as MC3 in NHPs, Moderna reported SM-102 as having improved tolerability NHPs. MRNA-GEN-00988589 at -591. One of Moderna's goals was "to improve vaccine tolerability without affecting vaccine potency". Hassett 2019 at 2. Moderna reported in Hassett that, "increased innate immune stimulation driven by the LNP is not necessary for increased immunogenicity, illustrating that we have an opportunity to improve vaccine tolerability without affecting vaccine potency". Hassett 2019 at 2.

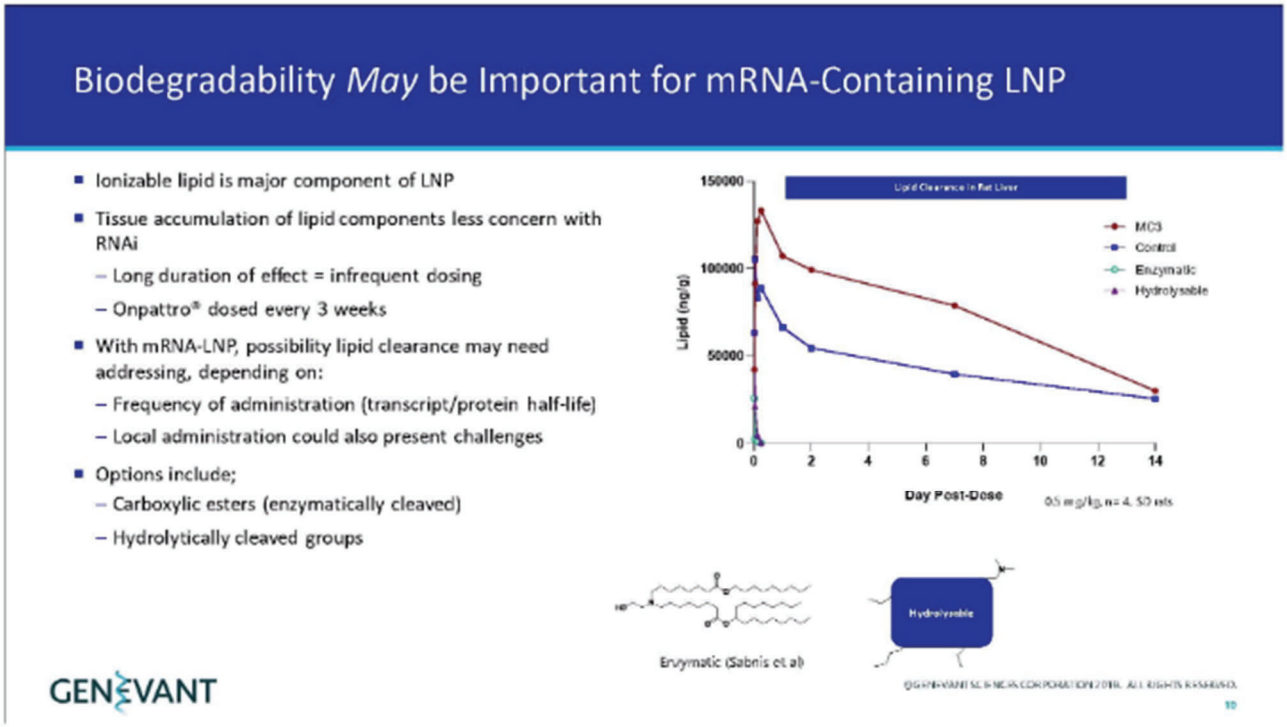
497. Moreover, NHPs in the MC3 group showed a stronger innate immune response compared to SM-102. Hassett 2019 at 5 ("NHPs in the MC3 group with the highest level of IL-6 also showed the highest level of edema, indicating a strong innate immune response in that individual animal."). NHPs in the MC3 group also have a stronger edema and erythema response compared to the SM-102 group after the first injection, and a stronger edema reaction compared to the SM-102 group after the second reaction. Hassett 2019 at 5; MRNA-GEN-00480514 at -514, Figure 7 and Figure 9.

498. Furthermore, as reported in Hassett 2019, Moderna found that in Sprague-Dawley rats, "MC3-formulated mRNA was the worst tolerated lipid tested, whereas lipid H (SM-102) was the best tolerated lipid tested (Figures 5F-5I)". Hassett 2019 at 6. In addition, "with the exception of IP-10 at the 0.01 mg dose, lipid H (SM-102) induced the lowest systemic cytokine production." Hassett 2019 at 6.

499. As explained above, SM-102 exhibited improved tolerability in NHPs, rats and mice. SM-102's increased biodegradability over MC3 informed Moderna's hypothesis that SM-

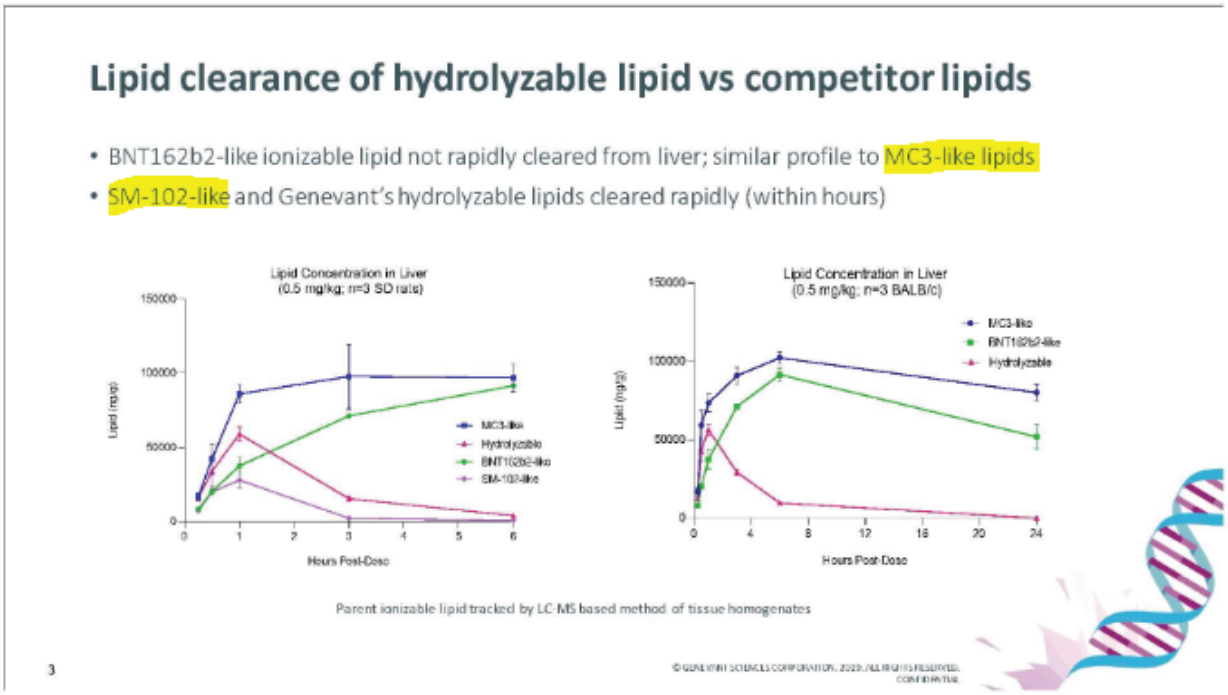
102 would exhibit increased tolerability as it would not remain at the injection site as long to elicit an immune response. Moreover, SM-102 also demonstrated similar immunogenicity as MC3. Although there is little correlation between expression and immunogenicity, expression and immunogenicity are two different readouts which inform vaccine efficacy. Hassett 4/26/2024 Tr. 68:20-69:1. Neither readout is solely indicative of vaccine efficacy.

500. Even Plaintiffs' documents acknowledge the significant difference that SM-102 and ionizable lipids made, including to potency and biodegradability. For example, a November 14, 2019 Genevant presentation titled "Strategies for the Delivery of Nucleic Acid Therapies" explains the importance of biodegradability for mRNA-Containing LNPs:



GENV-00285086 at 93-95. The presentation noted that "tissue accumulation of lipid components less concern with RNAi" and that "local administration could also present challenges" for mRNA-LNP; *see also* GENV-00286019 (presentation titled "Genevant's Biodegradable LNP Platform"); GENV-00286884 (presentation titled "Biodegradable LNP"). Further, a May 11, 2021 Genevant

presentation titled "Biodegradable LNP Platform" illustrates the advantages of "SM-10-like" lipids over "MC3-like lipids" with respect to lipid clearance:



GENV-00303059 at GENV-00303061 (annotated). This is consistent with my opinion that the way that 48.5 mol% SM-102 functions in the v1 Formulation is not equivalent to the way that the ≥50 mol % cationic lipid claimed in the Molar Ratio Patents functions.

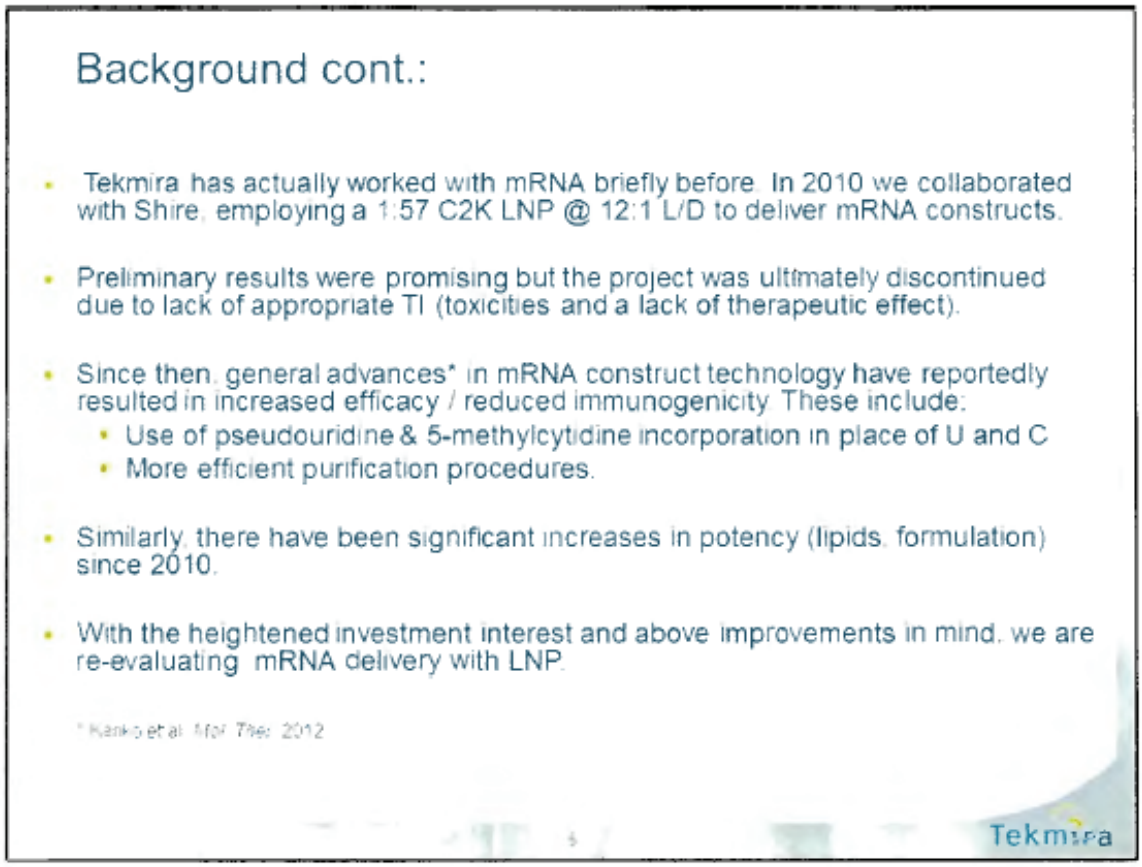
501. For example, the evidence shows that Moderna's lower concentration of its proprietary SM-102 cationic lipid (i.e. under 50 mol%) achieves improved tolerability for intramuscular doses and improved local protein expression. *See* Hassett 2019 at 6 ("MC3 formulated mRNA was the worst tolerated lipid tested whereas [SM-102] was the best tolerated lipid tested."); at 2 ("Many of our novel biodegradable lipids proved superior to MC3 for both protein expression and immunogenicity upon IM administration.'); at 8 ("The histopathology presented here for [SM-102], compared to that for MC3, is consistent with improved tolerability and reduced innate immune stimulation. The reduction in inflammatory cell infiltrate, myofiber

damage, and systemic cytokines support the hypothesis that mRNA vaccines may not require a strong adjuvant response for potent immune responses."). Local protein expression is important because the Accused Product is delivered intramuscularly, unlike the Molar Ratio Patents which are directed intravenous delivery. *See* MRNA-GEN-00018512 (Section 3.2.P.2 of the BLA titled "Pharmaceutical Development") at MRNA-GEN-00018513-4. Indeed, Moderna explained the importance of delivery mechanism to lipid selection:

> SM-102 is the ionizable lipid component of the SM-102 LNP. Under the acidic conditions of the encapsulation reaction, SM-102 provides a net positive charge to the LNP, which drives the spontaneous encapsulation of the negatively charged mRNA through electrostatic attraction. The concentration of SM-102 in the LNP was chosen to provide a stoichiometric excess of cationic charge and enable full charge complexation of the mRNA and efficient encapsulation.
>
> SM-102 is a biodegradable lipid. It was identified and developed through a screening process that examined the impact of a range of biodegradable lipids for protein expression and immunogenicity when injected by the intramuscular route. SM-102 was selected as the most potent lipid out of a panel of 30 ionizable lipids that were screened for expression and vaccine potency via the intramuscular (IM) route of administration in rodents. Finally, SM-102 was selected as the lead ionizable lipid due to improved tolerability over the lipids that were evaluated in non-human primates.

MRNA-GEN-00018512 (Section 3.2.P.2 of the BLA titled "Pharmaceutical Development") at MRNA-GEN-00018513-4.

502. In contrast, Plaintiffs' documents show that when they tried their own LNP with mRNA, they could not get an appropriate therapeutic index and had issues with toxicity such that their efforts were "ultimately discontinued":



Heyes Dep. Ex. 8 at 5. This is consistent with my opinion that the results achieved by 48.5 mol% SM-102 in Moderna's v1 Formulation are not equivalent to the results achieved by the cationic lipid mol % claimed in the Molar Ratio Patents.

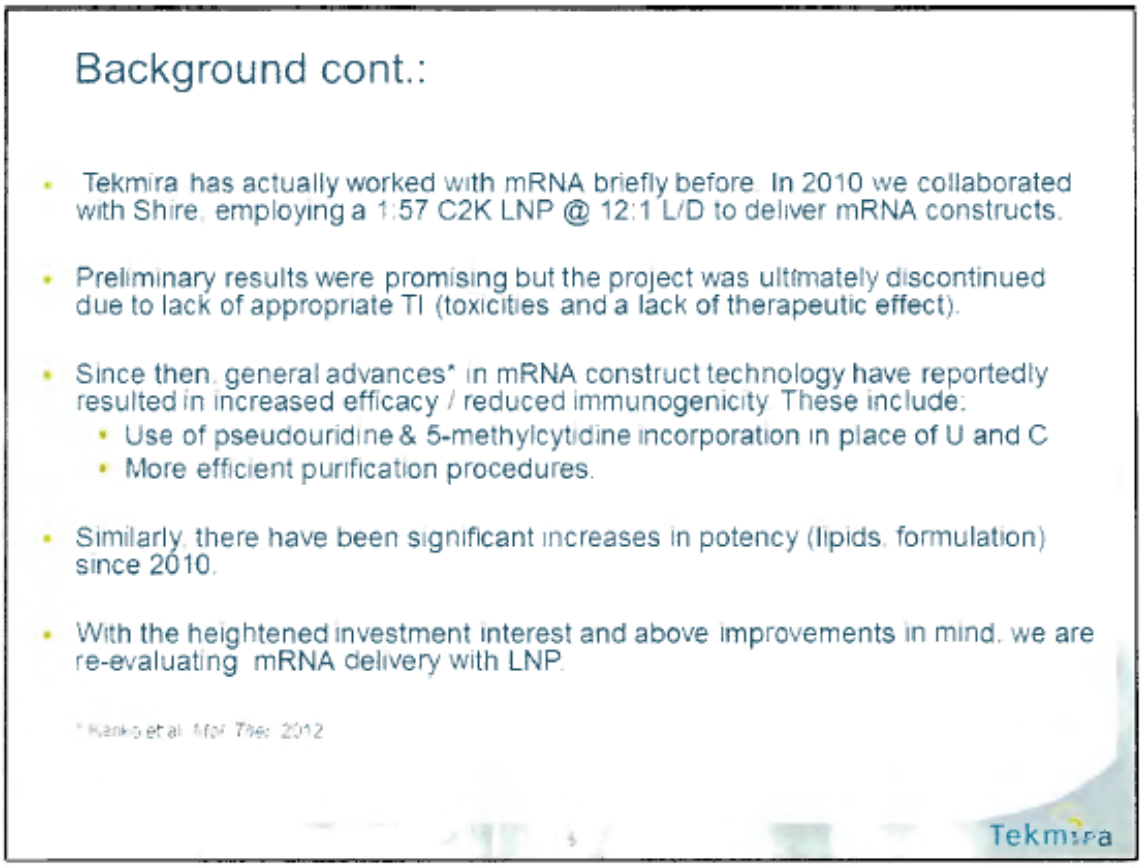
(D) Substantial Differences (≥50 mol% Cationic Lipid Range Limitations)

503. In my opinion, the physical and chemical properties of 48.5 mol % SM-102 cationic lipid in Moderna's SPIKEVAX® v1 Formulation are substantially different from the physical and chemical properties of the claimed ≥50 mol% cationic lipid ranges. This is consistent with the conclusions of my above analysis in terms of function, way, and result, which I incorporate by reference.

504. The substantial differences are explained by the specific mol % concentration of cationic lipid. For example, SM-102 does not comprise "alkyl chains with multiple sites of

unsaturation," which the Molar Ratio Patents explain are "useful for forming lipid particles with increased membrane fluidity." '069 Patent at 12:53-57. And the evidence shows that Moderna's SM-102 achieves improved tolerability for intramuscular doses and improved local protein expression as compared to MC3. *See* Hassett 2019 at 6 ("MC3 formulated mRNA was the worst tolerated lipid tested whereas [SM-102] was the best tolerated lipid tested."); at 2 ("Many of our novel biodegradable lipids proved superior to MC3 for both protein expression and immunogenicity upon IM administration."); at 8 ("The histopathology presented here for [SM-102], compared to that for MC3, is consistent with improved tolerability and reduced innate immune stimulation. The reduction in inflammatory cell infiltrate, myofiber damage, and systemic cytokines support the hypothesis that mRNA vaccines may not require a strong adjuvant response for potent immune responses."). Moreover, these differences are important because Moderna's SPIKEVAX® delivers mRNA intramuscularly, unlike the Molar Ratio Patents which are directed to intravenous delivery of siRNA. Indeed, Plaintiffs' documents show that when they tried their

own LNP with mRNA, they could not get a therapeutic index and had issues with toxicity.



Heyes Dep. Ex. 8 at 5.

505. Additionally, Dr. Mitchell does not acknowledge that in his opinion, the v1 formulation infringes under the doctrine of equivalents despite not meeting up to two distinct claim elements literally: limitations of the '435 Patent claims requiring less than 49.5 mol% non-cationic lipid, and the limitations of '435, '069, '668 and '359 claims requiring more than 50 mol% cationic lipid. The fact that Moderna's v1 formulation does not literally meet multiple independent and distinct limitations in these asserted claims further supports my opinion that the differences are far more than substantial.

506. In sum, the evidence that I discuss above in the function/way/result framework shows that the 48.5 mol % SM-102 cationic lipid concentration in Moderna's SPIKEVAX® v1

Formulation is substantially different from claimed cationic lipids and lipid ranges in the Molar Ratio Patents with respect to their physical and chemical properties.

iii. Prosecution History Estoppel (≥50 mol% Cationic Lipid Range Limitations)

507. In my opinion, prosecution history estoppel precludes Plaintiffs' arguments that Moderna's v1 Formulation infringes all Asserted Claims of the '069, '359, '668, and '435 patents requiring "from 50 mol % to 65 mol %" or "from 50 mol % to 85 mol %" of a cationic lipid (including dependent claims reciting narrower ranges) under the doctrine of equivalents based on narrowing claim amendments and based on arguments during prosecution that would lead a competitor to rely on disclaimers of claim scope by the applicant of cationic lipids less than 50 mol% cationic lipid.

508. In my opinion, the applicant amended their patent claims to be narrower and did so for the purpose of patentability. During prosecution of the '069 patent, the examiner rejected the claims as being anticipated by MacLachlan, et al. (US 2006/0008910), which "teaches the SNALP wherein the cationic lipid is from about 2 mol % to about 60 mol % of the total lipid present in the particle (paragraph 85), the phospholipid is from about 5% to about 90% or from about 10% to about 85% of the total lipid present in the particle (paragraph 85), the cholesterol is from about 20% to about 55% of the total lipid present in the particle (paragraph 85, top of page 8), and the conjugated lipid is from about 1 % to about 20% of the total lipid present in the particle (paragraph 85)." '069 File History May 12, 2011 at 2-4. The examiner tied the rejection to the inclusion of "about" in the claims explaining:

> The claims are further directed to the particle wherein the nucleic acid is a siRNA, the relative amounts of components read on a broad range of amounts because of the term 'comprising about'. The applicants do not provide a definition of the term in the specification. Thus, 'comprising about' could embrace an amount+/- 10, 20, 30 mol % of a lipid component.

'069 File History May 12, 2011 at 2. The examiner further provided a comparison of the lipid components in the application and MacLachlan:

Application	MacLachlan
instant claims of '367 1) cationic lipid comprising from about 50-65 mol % 2) phospholipid comprises from about 4-10 mol % 3) cholesterol comprising from about 30-40 mol% 4) conjugated lipid comprising from about 0.5-2 mol%	pre-grant US publication (paragraph 0085) 1) cationic lipid 2-60, 5-50, 10-45, 20-40, 30 mol% 2) phospholipid 5-90 mol% 3) cholesterol 20-55 mol % 4) conjugated lipid 1-20 mol %

'069 File History May 12, 2011 at 3-4. The examiner further rejected pending claims as obvious in view of Maclachlan, et al. (US 2006/0008910) and further in view of Fosnaugh, et al. (US 2003/0143732). '069 File History May 12, 2011 at 5-6. The examiner explained:

> In response to applicant's argument that Fosnaugh and Maclachlan do not teach or suggest 1:57 SNALP formulation and their new and unexpected results, the argument is not found persuasive because while it is acknowledged that 1 :57 shows a new an unexpected result, the product recited in ***the instant claims read on broad range of SNALP formulations***, including 2:30 and 2:40 ***because of the term 'comprising from about'***. The term is broad because the specification does not provide a definition of the term and the term could read on SNALP formulations other than 1:57, e.g., 2:30 and 2:40.

'069 File History May 12, 2011 at 6 (emphasis added). The examiner further rejected pending claims as invalid for obviousness-type double patenting over reference claims that recited overlapping ranges. '069 File History May 12, 2011 at 7-14. After examiner interviews, the applicant amended the claims to remove "about":

1. (Currently amended) A nucleic acid-lipid particle comprising:

(a) a nucleic acid;

(b) a cationic lipid comprising from ~~about~~ 50 mol % to ~~about~~ 65 mol % of the total lipid present in the particle;

(c) a non-cationic lipid comprising a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the phospholipid comprises from ~~about~~ 4 mol % to ~~about~~ 10 mol % of the total lipid present in the particle and the cholesterol or derivative thereof comprises from ~~about~~ 30 mol % to ~~about~~ 40 mol % of the total lipid present in the particle; and

(d) a conjugated lipid that inhibits aggregation of particles comprising from ~~about~~ 0.5 mol % to ~~about~~ 2 mol % of the total lipid present in the particle.

'069 File History Aug. 11, 2011 at 2. The applicant explained:

> During the interview, Applicants' representatives proposed amending the claims to delete the word 'about' from the ranges of lipid components and argued that the claimed ranges were not anticipated by MacLachlan *et al.* (US2006/0008910) because that reference failed to disclose the claimed ranges with sufficient specificity as required by M.P.E.P 2131.03 (II) and *Atofina*.

'069 File History Aug. 11, 2011 at 6. The applicant argued:

> In making both rejections, the Examiner alleges that the term 'comprising from about' recited in the instant claims embraces a broad range of lipid components. In an earnest effort to expedite prosecution, but without acquiescing on the merits of the rejection, Applicants have amended the claims to delete 'about' from the ranges of lipid components recited therein.

'069 File History Aug. 11, 2011 at 7. The applicant further provided a comparison of the ranges of lipid components in the amended claims and MacLachlan:

Lipid Component	Claim 1 as Amended	US 2006/0008910*
Cationic Lipid	50-65 mol %	"2-60, 5-50, 10-45, 20-40, 30 mol%"
Phospholipid	4-10 mol %	"5-90 mol%"
Cholesterol	30-40 mol %	"20-55 mol %"
Conjugated Lipid	0.5-2 mol %	"1-20 mol %"

*The ranges set forth in this column are reproduced from page 4 of the Office Action mailed May 12, 2011.

'069 File History Aug. 11, 2011 at 8. The applicant did not provide another definition of "about" when responding to the Examiner. I understand that Plaintiffs argued, and the Court accepted, that "about" in the context of the intrinsic record means "+/- 10, 20, 30 mol % of a lipid component." *See* D.I. 266 (Memorandum Opinion re Claim Construction) at n. 7; *see also* Plaintiffs' Markman Presentation at slides 31–36.

509. Further, during prosecution of the '069 patent, the examiner explained:

> It is clear from the specification that the present invention is based, in part, on the surprising discovery that 1:57 SNALP formulations provide new and unexpected results when used for the *in vitro* or *in vivo* delivery of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA). More particularly, Applicants have found that SNALP formulations having **increased** amounts of cationic lipid, *e.g.*, one or more cationic lipids comprising from about 50 mol % to about 65 mol % of the total lipid present in the particle, provide ***unexpectedly superior advantages*** when used for the *in vitro* or *in vivo* delivery of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA).

510. '069 File History Jan. 31, 2011 at 9; *see also* '069 File History Jan. 31, 2011 at 6–12 (arguing the amendments overcame other rejections including obviousness-type double patenting). Ultimately, the examiner explained in the Notice of Allowance that the narrowed ranges of molar ratios was the sole basis for allowance: "The prior art of record is considered pertinent to applicant's disclosure. US 6,815,432, cited on an IDS discloses lipid formulations but does not appear to disclose the ranges for each of the lipids recited in the instant claims." *See* '069 Notice of Allowance at 6. A POSA would understand from this that the arguments and amendment deleting the word "about" were made to overcome rejections from the Examiner, including prior-art rejections, and that the arguments and amendments were successful in getting the claims allowed by the Examiner (in other words, those amendments and arguments were clearly made for purposes of patentability).

511. Similarly, the applicant amended their patent claims of the '359, '668, and '435 patents to be narrower and did so for the purpose of patentability. Plaintiffs are estopped from

asserting the doctrine of equivalents to capture less than 50 mol % of a cationic lipid for the '359, '668, and '435 patents because during prosecution of the '359 and '668 patents, the applicants filed preliminary amendments to delete "about" from original claims reciting "a cationic lipid comprising from about 50 mol % to about 65 mol % of the total lipid." *See, e.g.,* '359 File History Oct. 5, 2011 at 114, Amdt. Dated Mar. 28, 2012 at 4; '668 P.H Jun. 26, 2013 at 114, Nov. 6, 2013 at 5. And during prosecution of the '435 patent, the applicants filed preliminary amendments to delete "about" from original claims reciting "a cationic lipid comprising from about 50 mol % to about 85 mol % of the total lipid." *See, e.g.,* '435 File History Aug. 18, 2014 at 114, Feb. 26, 2015 at 2. Without these amendments, applicant would have known from the earlier '069 prosecution that the claims would face rejection again over the prior art, confirming the amendments were made for patentability. Plaintiffs are also estopped from arguing Moderna's v1 Formulation infringes any Asserted Claims of the '359, '668, and '435 patents requiring from 50 mol % to 65 or 85 mol % of a cationic lipid under the doctrine of equivalents because the '359, '668, and '435 patents are issued from continuation applications of the '069 patent and use the same claim terms as in the '069 patent (reciting cationic lipid amounts in mol % ranges), which lack the word "about," which a POSA would understand would carry the same meaning. At no point during prosecution of the later '359, '668, and '435 patents did the applicant inform the Examiner that the disclaimer was withdrawn, and that the pending claims in those later patent applications needed to be examined again in light of the prior art such as MacLachlan.

512. I understand that when surrendering claim scope for reasons related to patentability, as the applicant did here, there is a presumption that applicant has surrendered everything between the original claim limitation and the amended claim limitation. The applicant never responded to the examiner to state that it intended to disclaim any amount less than +/-30% variability.

Therefore, when the applicant disclaimed "about" (which examiner defined as +/-10/20/30%), it disclaimed every variation leading up to that (*e.g.*, +/- 0.00001% to +/-30). I further understand that the Court has already found that by removing the word "about," the applicant disclaimed variability of "+/- 10, 20, 30 mol %" from the claims. D.I. 266 (Memorandum Opinion re Claim Construction) at 21 ("a claimed range of 'about' 50–65 mol % could potentially encompass a range as small as 40–75 mol % and as large as 20–95 mol %.[7] When Plaintiff removed the phrase 'comprising about,' it only ***clearly disclaimed these broader ranges*** and not the scientific conventions of rounding") (emphasis added).

513. Based on the Examiner's definition of "about", which the applicant accepted, the claims before and after the amendment are as follows:[43]

	Original claim 1 as of 1/31/2011	**Amended claim**	**Scope of surrendered territory**	**v1 Formulation**
Cationic Lipid	About 50 mol % to about 65 mol % (20 to 95 mol %)	50 mol % to 65 mol %	<50 mol % and 65 to 95 mol %	48.5 mol %
Phospholipid	About 4 mol % to about 10 mol % (0.0 to 40 mol %)	4 mol % to 10 mol %	<4 mol % and 10 to 40 mol %	11.1 mol %
Cholesterol	About 30 mol % to about 40 mol % (0.0 to 70 mol %)	30 mol % to 40 mol %	<30 mol % and 40 to 70 mol %	38.9 mol %
Conjugated lipid	About 0.5 to about 2 mol% (0.0 to 32 mol %)	0.5 mol % to 2 mol %	>2 to 32 mol%	1.5 mol %

[43] As noted above at ¶ 312, throughout this section I do not explicitly refer to rounding for simplicity, but I do apply the Court's claim construction.

As shown above, Moderna's v1 Formulation has a 48.5 mol % cationic lipid, which falls within the scope of the surrendered territory. Although I show the '069 claims above as an example, the same analysis applies for the related '435, '668, '359 patents.

514. In my opinion, a nucleic acid-lipid particle comprising 48 mol % cationic lipid (or any amount between 45 mol % and 50 mol %) was foreseeable to a POSA at the time the applicant made their narrowing amendment. As demonstrated in the file history, the prior art disclosed incremental percentages of lipid components in nucleic acid-lipid particles. *See, e.g.*, '069 File History May 12, 2011 at 3-4 (summarizing disclosures of MacLachlan, U.S. 2006/0008910); '069 File History Aug. 11, 2011 at 8 (same). During prosecution, the examiner also explained:

> In response to applicant's argument that Fosnaugh and Maclachlan do not teach or suggest 1:57 SNALP formulation and their new and unexpected results, the argument is not found persuasive because while it is acknowledged that 1 :57 shows a new an unexpected result, the product recited in ***the instant claims read on broad range of SNALP formulations***, including 2:30 and 2:40 ***because of the term 'comprising from about'***. The term is broad because the specification does not provide a definition of the term and the term could read on SNALP formulations other than 1:57, e.g., 2:30 and 2:40.

'069 File History May 12, 2011 at 6 (emphasis added). This explanation further supports estoppel because it shows that the equivalents were foreseeable. In other words, the applicant already had an earlier patent to the 2:40 formulation with overlapping ranges, as raised by the examiner, showing that the applicant knew that other ranges existed, such as 48 mol % cationic lipid, and chose to disclaim it. Likewise, the specification of the '069 Patent was drafted with incremental percentages, showing the ability to describe incremental variation in lipid mol %. *See, e.g.*, '069 Patent at 18:40–19:2.

515. Additionally, based on my review of the file histories, the applicant's reasons for the claim amendments were not tangential to the alleged equivalent (i.e., nucleic acid-lipid particles comprising <50 mol % cationic lipid). As I described above, these claim amendments to

remove "about" were made to overcome rejections of the prior art that taught overlapping ranges of mol % cationic lipid, and specifically an embodiment comprising about 40 mol% cationic lipid referred to as the "2:40" formulation. Nor do I see another reason that would have prevented Plaintiffs from describing and claiming nucleic acid-lipid particles comprising lower mole percentages of cationic lipid. As I described above, nucleic acid-lipid particles comprising varying amounts and ranges of cationic lipid were routinely described in the prior art and Plaintiffs were capable of doing so in the specification. When the applicant wanted to seek claims to lipid particles with lower amounts of cationic lipid, they were clearly able to do so. *See* '378 Patent Claim 1 (with no lower limit on the cationic lipid).

516. Reviewing the arguments the applicant made about the alleged unexpected results of nucleic acid-lipid particles comprising greater than 50 mol % cationic lipid as well as the arguments made when amending the claim described above, as well as emphasizing the narrowness of the claims compared to the prior art overlapping ranges, a competitor would reasonably believe that Plaintiffs were effectively surrendering and disclaiming nucleic acid-lipid particles comprising less than 50 mol % cationic lipid.

517. Further supporting the argument-based estoppel, Plaintiffs also argued to the Patent Office that the alleged unexpected results and purported innovative aspects of the invention arising from "high levels of cationic lipids" to try to distinguish prior art. For example, during the '069 patent IPR, Plaintiffs alleged:

> The '069 patent Is directed to the ***surprising discovery that nucleic acid-lipid particle formulations with high levels of cationic lipids and low levels of conjugated lipids*** exhibit favorable in vivo transfection efficiencies as well as "improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index [a measure of dosage relative to toxic effect] as compared to nucleic acid-lipid particle compositions previously described." . . . ***Reflecting this discovery, the '069 patent claims nucleic acid-lipid particle formulations with high levels of cationic lipids (50–65 mol %) and low levels of conjugated lipids***

> ***(0.5–2 mol %)***—as well as specific levels of cholesterol/derivative (30-40 mol %) and phospholipid (4-10 mol %).

See, e.g., IPR2019-00554, Paper 7 (Patent Owner's Preliminary Response) at 13, 14, 34, 45–46 (emphasis added); id., Paper 15 (Patent Owner's Response) at 7, 8, 29–30, 32, 62, 64. During the IPR for the '435 patent, Plaintiffs again alleged:

> The '435 patent discloses the ***"surprising discovery" that nucleic acid-lipid particle formulations with a high level of cationic lipid and a remarkably low level of conjugated lipid*** exhibited favorable in vivo transfection efficiencies as well as "improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index [a measure of dosage relative to toxic effect] as compared to nucleic acid-lipid particle compositions previously described." . . . ***Reflective of this discovery, the '435 patent claims nucleic acid-lipid particle formulations with a high level of cationic lipid (50–85 mol %) and an unconventionally low level of conjugated lipid (0.5–2 mol %).***

See, e.g., IPR2018-00739, Paper 12 (Patent Owner's Preliminary Response) at 2, 6–8, 12, 24, 26, 37 (emphasis added); id., Paper 24 (Patent Owner's Response) at 2, 14, 19–21, 24, 32, 47, 54–55. These statements would also apply to the '359 and '668 patents, which are in the same patent family and likewise claim "high levels of cationic lipids (50–65 mol %)." From these arguments, a competitor would reasonably believe that Plaintiffs were effectively surrendering and disclaiming nucleic acid-lipid particles comprising less than 50 mol % cationic lipid. It is my understanding that these arguments preclude Plaintiffs from now recapturing nucleic acid-lipid particles claimed with less than 50 mol % cationic lipid under the '069, '435, '359 and '668 patents.

iv. Public Dedication

518. Plaintiffs are precluded from asserting that any Asserted Claims of the '069, '359, '668, and '435 patents cover the v1 Formulation under the doctrine of equivalents because the specification of the patents discloses the unclaimed subject matter such that it has been dedicated to the public. For example, the '069 patent specification discloses embodiments with cationic lipid comprising ranges of "about 50 mol %" or more of the total lipid:

> In some embodiments, the cationic lipid may comprise from ***about*** 50 mol % to about 90 mol %, from about 50 mol % to about 85 mol %, from about 50 mol % to about 80 mol %, from about 50 mol % to about 75 mol %, from about 50 mol % to about 70 mol %, from about 50 mol % to about 65 mol %, or from about 50 mol % to about 60 mol % of the total lipid present in the particle.

See, e.g., '069 patent at 18:40–46 (emphasis added).[44] As detailed above, during prosecution of the '069 patent, the examiner defined "about" as "+/-***20, 30 mol % of a lipid component***." '069 File History May 12, 2011 at 2. The above passage in the specification would therefore be understood to refer to embodiments with 20 mol % to 100 mol % cationic lipid. Additionally, during the claim construction phase of this case, I understand that Plaintiffs relied on the specification containing "embodiments [that] comprise less than 50mol% cationic lipid. Plaintiffs' Markman Presentation at slides 84 and 104–105 (citing '378 Patent at 20:19-34, 52:59-63). The specification discloses embodiments with 45–50mol% cationic lipid, which is the scope of equivalence Plaintiffs now seek to capture through the doctrine of equivalents. Because these were disclosed in the specification but not claimed in the '069, '359, '668, and '435 patents, in my opinion a POSA would understand that the applicant dedicated such embodiments to the public.

519. My opinion that the applicant surrendered this claim scope is also supported by applicant's statements in the specification and the file history distinguishing the present invention from the prior art 2:40 formulation, which was described as inferior. *See, e.g.*, '069 patent at 5:66–6:3 ("FIG. 2 of Example 3 shows that the "1:57 SNALP" formulation was substantially more effective at silencing the expression of a target gene as compared to nucleic acid-lipid particles previously described ("2:40 SNALP")."); '069 File History Jan. 31, 2011 at 10 (similar); '069 File History Aug. 11, 2011 at 9–10 (similar). Moderna's LNP with 48.5 mol % cationic lipid is far

[44] The '069, '359, '668, and '435 patents are in the same family and share the same specification.

closer to the 40 mol% cationic lipid in the supposedly inferior prior art 2:40 formulation than the 1:57 embodiment in the Molar Ratio Patents, which contains 57 mol% cationic lipid.

520. My opinions are reinforced by the later '378 Patent, in which Plaintiffs obtained a patent with no lower limit on the cationic lipid, thus covering the embodiments it chose ***not*** to claim in the earlier family members (i.e. '069, '359, '668, and '435 patents).

521. Because the issued '069, '359, '668, and '435 patents claim a nucleic acid-lipid particle comprising a cationic lipid comprising "from 50 mol % to 65 mol %" or "from 50 mol % to 85 mol %" of the total lipid in the particle, while the specification discloses from >20 mol % cationic lipid, Plaintiffs are estopped from enforcing any unclaimed embodiments comprising 20 to 50 mol % of a cationic lipid, as that scope has been dedicated to the public.

v. Vitiation

522. I understand a claim term is vitiated when the proposed equivalent embraces a structure that is specifically excluded from the scope of the claims. As explained above, the applicant disclaimed embodiments comprising less than 50 mol % of a cationic lipid and the examiner explained in the Notice of Allowance for the '069 patent that the narrowed ranges of molar ratios was the sole basis for allowance:

> The prior art of record is considered pertinent to applicant's disclosure. US 6,815,432, cited on an IDS discloses lipid formulations but does not appear to disclose the ranges for each of the lipids recited in the instant claims.

'069 Notice of Allowance at 6. Vitiating the numerical limitations requiring a cationic lipid at specified mol % ranges, as would be required under Plaintiffs' theories of infringement under the doctrine of equivalents, would deprive the public of the notice function of the claims and thereby render the claims meaningless. I incorporate my function-way-result analysis above, which further supports my opinion. Thus, in my opinion, Plaintiffs are precluded from claiming that that

Moderna's v1 Formulation infringes any Asserted Claims of the '069, '359, '668, and '435 patents under the doctrine of equivalents.

523. I note that Dr. Mitchell does not explain why prosecution history estoppel, vitiation, and/or public dedication should not apply in this instance. To the extent Dr. Mitchell does so later, I reserve the right to respond.

4. Moderna's SPIKEVAX® v2 Formulation Does Not Meet the Cationic Lipid or PEG Range Limitations of the Molar Ratio Patents

524. Moderna's SPIKEVAX® v2 Formulation does not infringe the Asserted Claims of the Molar Ratio Patents at least because it does not meet the cationic lipid range limitations or the PEG range limitations literally or under the doctrine of equivalents.

a. No Literal Infringement of ≥50 mol% Cationic Lipid Limitation

525. I incorporate by reference Section X.D.3.a above.

526. Briefly, as I explain above, the inputs into the manufacturing process are the best evidence of the composition of the resulting particles in Moderna's COVID-19 vaccine. The target v2 Formulation is 48.0:38.5:11.0:2.5.

b. No Literal Infringement of PEG Limitation

527. The Asserted Claims of the '069, '359, '668, and '435 patents recite or incorporate a limitation requiring a nucleic acid-lipid particle comprising "a conjugated lipid . . . comprising from 0.5 mol % to 2 mol % of the total lipid present in the particle," and the Asserted Claims of the '378 patent recite or incorporate a limitation requiring "a nucleic acid-lipid particle consisting essentially of" "a polyethyleneglycol (PEG)-lipid conjugate consisting of from 0.1 mol % to 2 mol % of the total lipid present in the particle."

528. I incorporate by reference Section X.D.3.a above.

529. Briefly, as I explain above, input values are the best evidence of the composition of the resulting particles in Moderna's COVID-19 vaccine. There is no dispute that the two target formulations at issue are: 48.5:38.9:11.1:1.5 (v.1) and 48.0:38.5:11.0:2.5 (v.2). Focusing on Moderna's v2 Formulation, which comprises 2.5 mol% PEG, it does not meet the claim limitations requiring from 0.5 mol % to 2 mol % of a conjugated lipid or from 0.1 mol % to 2 mol % of PEG-lipid conjugate. Moderna's v2 Formulation therefore does not literally infringe any Asserted Claim of the '069, '359, '668, '435, and '378 patents.

530. Dr. Mitchell also states that "Moderna's witnesses are not aware of any significant differences with respect to the different part numbers assigned to its COVID-19 vaccine, ***whether formulated using the v1 or v2 Formulation***, including part numbers assigned for different manufacturing processes, scales, or manufacturing locations." Mitchell Rep. ¶355 (emphasis added). I disagree and further note that the testimony Dr. Mitchell cites as alleged support does not support his statement that Moderna's witnesses could point to no significant differences between the v1 and v2 Formulations in particular. In fact, as is apparent from Dr. Mitchell's own choice quotations included in paragraph 355, the witness was asked about, for example, changes in scale, manufacturing facility, or use of different mixers, but not whether changing the molar ratios of the lipids would cause "significant differences." And, contrary to Dr. Mitchell's suggestion, numerous Moderna witnesses were asked about and readily explained the differences made by increasing the molar percentage of the PEG, for example, in going from v1 to v2. *See, e.g.*, Section VIII.A.4 above.

c. No Infringement of ≥50 mol% Cationic Lipid Range Limitations Under Doctrine of Equivalents

531. In my opinion, the SM-102 cationic lipids and the specific mol % therefore in Moderna's SPIKEVAX® v2 Formulation have different functions, ways, and results, and are

substantially different from the claimed lipids at the lipid molar ratios claimed in the Molar Ratio Patents. I incorporate by reference Section X.D.3.b above.

532. For the reasons explained in Sections X.D.1 and X.D.3.a, under Plaintiffs' view of the claims and Plaintiffs' new infringement theory that focuses on the lipid content of individual lipid particles, the Certificates of Analysis do not provide evidence of the lipid content of any individual particle, and do not show that the particles meet Plaintiffs' hypothetical claims.

i. Dr. Mitchell's DOE Analysis

(A) Function (≥50 mol% Cationic Lipid Range Limitations).

533. Dr. Mitchell conflates equivalence of the function of the cationic lipid broadly with the function of the specific claimed cationic lipid mol %. While I do not disagree with Dr. Mitchell's broad statement that the SM-102 cationic lipids in the Accused Products "provide a positive electrostatic charge that subsequently interacts with the negative charge of the nucleic acid to facilitate encapsulation of the nucleic acid," I disagree with his conclusion that "[t]he function of the SM-102 cationic lipid and its mol % concentration in drug product lots of the Accused Product, including within lots formulated with the PVU, v1, and v2 Formulations, is substantially the same as the cationic lipid and its mol % in the claimed invention." Mitchell Rep. ¶¶ 656-657. Dr. Mitchell's conclusion relies on Moderna's statements to the FDA that [redacted] Mitchell Rep. ¶ 657 citing MRNA-GEN-00988461 at -468. Dr. Mitchell opines that the function of the SM-102 cationic lipid and its mol % concentration in the v1 and v2 Formulation is equivalent because Moderna's description, which would apply to any LNP

encapsulating mRNA, "remained constant throughout Moderna's regulatory submissions, notwithstanding the change in the target cationic lipid mol % in the v1 and v2 formulations." Mitchell Rep. ¶ 657. This fails to address the impacts of changing the cationic lipid mol % concentration, discussed below at Section X.D.4.c.ii.

(B) Way (≥50 mol% Cationic Lipid Range Limitations).

534. Dr. Mitchell's finding that "the SM-102 cationic lipid and its mol % concentration in drug product lots of the Accused Product, including within lots formulated with the PVU, v1, and v2 Formulations, [] perform[s] substantially the same function of the cationic lipid of the Asserted Claims, including its recited mol %, in substantially the same way" is conclusory. Mitchell Rep. ¶ 659. Dr. Mitchell articulates only that "[t]he way in which the SM-102 lipids of the drug product achieve their function is through their structure, chemical composition, and concentration, which enables the lipids to carry a positive charge in acidic conditions and subsequently helps to drive interactions, including with the nucleic acid during encapsulation" and that "the SM-102 lipids in all lots of Moderna's COVID-19 vaccine drug product, regardless of the target or measured mol % of SM-102 in that lot, are the same structure and possess the same structural features." Mitchell Rep. ¶¶ 659-660. Dr. Mitchell does not compare any specific structural features between Moderna's PVU, v1 and v2 Formulations.

(C) Result (≥50 mol% Cationic Lipid Range Limitations).

535. Dr. Mitchell's finding that "the SM-102 cationic lipid and its mol % concentration in drug product lots of the Accused Product, including within lots formulated with the PVU, v1, and v2 Formulations achieve substantially the same result as the cationic lipid and its mol % in the claimed invention" likewise relies on the overbroad premise that "the result of the cationic lipid limitation, including its recited mol % in the claims, in the context of the invention as a whole, is

the effective and efficient intracellular delivery of nucleic acid." Mitchell Rep. ¶ 661. Again, this would apply broadly to LNPs encapsulating nucleic acid. Dr. Mitchell opines that "Moderna's COVID-19 vaccine drug product, whether formulated with the PVU, v1, or v2 Formulations, including drug product formulations with reported cationic lipid content values of 45 to 50 mol % cationic lipid, achieve substantially the same result, including with respect to efficacy (immunogenicity), safety, and stability compared to formulations using 50 mol % cationic lipid . . . ." Mitchell Rep. ¶ 661. But in support of his opinion, Dr. Mitchell conflates clinical equivalency and chemical equivalency. For example, Dr. Mitchell cites Don Parsons' testimony: [redacted] Mitchell Rep. ¶ 661 citing Parsons 6/7/2024 Dep. Tr. at 202:17-203:4 (emphasis added). And Dr. Mitchell cites an e-mail chain [redacted], but takes it out of context and does not account for e-mails later in the chain that [redacted]." Mitchell Rep. ¶ 662 citing MRNA-GEN-00601091.

536. Dr. Mitchell also fails to address evidence showing, for example, [redacted]." MRNA-GEN-00539393 at MRNA-GEN-00539397; *see also* MRNA-GEN-00533651 at MRNA-GEN-00533662 [redacted].

(D) Substantial Differences (≥50 mol% Cationic Lipid Range Limitations).

537. I disagree with Dr. Mitchell's opinion that "the cationic lipid content of each lot of Moderna's COVID-19 drug product, including lots formulated with the PVU, v1, and v2 Formulations, are insubstantially different both from one another and insubstantially different from the claimed cationic lipid mol % limitation." Mitchell Rep. ¶ 667. Dr. Mitchell states that "Moderna's express goal when changing its formulation of various vaccine programs in the 2018-2019 timeframe and again in 2020 for the COVID-19 vaccine drug product was to create a product that was insubstantially different from its formulations with 50 mol % cationic lipid in order to avoid the need to conduct additional clinical trials." Mitchell Rep. ¶ 669. But the FDA's concepts of equivalents, comparability, and bioequivalence are different than the theory of patent infringement by the doctrine of equivalents. *See* Godshalk Rep. §§ V, VI.

(E) Hypothetical Claims (≥50 mol% Cationic Lipid Range Limitations).

538. I understand that the doctrine of equivalents analysis may be conducted by constructing a "hypothetical claim" and assessing whether the Accused Product would literally infringe that claim. Dr. Mitchell opines that a "potential 'hypothetical claim' would recite a nucleic acid-lipid particle where the lower limit on the amount of cationic lipid is 45 mol %, rather than 50 mol %." Mitchell Rep. ¶ 679. For the reasons explained above, I disagree with Dr. Mitchell's predicate statement that "Moderna concluded that there is no difference when the target amount of cationic lipid is [redacted] and with his findings based on that false premise. Mitchell Rep. ¶ 679.

539. Additionally, for the reasons explained in Sections X.D.1 and X.D.3.a, under Plaintiffs' view of the claims and Plaintiffs' new infringement theory that focuses on the lipid content of individual lipid particles, the Certificates of Analysis do not provide evidence of the

lipid content of any individual particle, and do not show that any individual particles meet Plaintiffs' and Dr. Mitchell's hypothetical claims.

ii. My Function-Way-Result Analysis

540. In my opinion, the 48.0 mol % SM-102 cationic lipid in Moderna's SPIKEVAX® v2 Formulation has a different function, way, and result, and is substantially different from, the claimed ≥50 mol % cationic lipid ranges in the Molar Ratio Patents. Additionally, although I refer below to Moderna's target v2 Formulation with 48.0 mol % SM-102 cationic lipid, Dr. Mitchell also contends that the claim extends to 45 mol % cationic lipid under the doctrine of equivalents, which I considered as part of my analysis.

(A) Function (≥50 mol% Cationic Lipid Range Limitations).

541. In my opinion, the ≥50 mol % cationic lipids claimed in the Molar Ratio Patents serve different functions as compared to the 48.0 mol % SM-102 in the v2 Formulation. At a high level, the higher level (i.e. ≥50 mol %) of cationic lipid claimed in the Molar Ratio Patents forms lipid particles with increased membrane fluidity to efficiently deliver siRNA to distal sites (e.g. tumor). Meanwhile, the 48.0 mol % SM-102 in the v2 Formulation promotes rapid degradation at the local site of injection (i.e. the arm) with intramuscular delivery.

(1) The Function of the ≥50 mol% Cationic Lipid Range Limitations in the Asserted Claims

542. The specification of the Molar Ratio Patents explains that there are distinct benefits of using 50 mol % or more of a cationic lipid and that these distinct benefits were material to the patentability of the Molar Ratio Patents. Specifically, the specification explains: "***The present invention is based, in part, upon the surprising discovery that lipid particles comprising from about 50 mol % to about 85 mol % of a cationic lipid***, from about 13 mol % to about 49.5 mol %

of a non-cationic lipid, and from about 0.5 mol % to about 2 mol % of a lipid conjugate ***provide advantages when used for the in vitro or in vivo delivery of an active agent, such as a therapeutic nucleic acid (e.g., an interfering RNA).***" '378 Patent at 6:6-13 (emphasis added). Regarding the function of the ≥50 mol% cationic lipid in the Asserted Claims, the specification of the Molar Ratio Patents explains: "It has surprisingly been found that cationic lipids comprising alkyl chains with multiple sites of unsaturation, e.g., at least two or three sites of unsaturation, are particularly useful for forming lipid particles with increased membrane fluidity." '069 Patent at 12:53-57. A POSA would understand from these teachings that >50 mol% cationic lipid had the function of Forms lipid particles with increased membrane fluidity to efficiently deliver siRNA to distal sites.

543. The prosecution history of the Molar Ratio Patents further supports the distinct benefits of 50 mol % or more of a cationic lipid in an LNP. During prosecution of the '069 patent, the examiner explained: "It is clear from the specification that the present invention is based, in part, on the surprising discovery that 1:57 SNALP formulations provide new and unexpected results when used for the *in vitro* or *in vivo* delivery of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA). More particularly, Applicants have found that SNALP formulations having **increased** amounts of cationic lipid, *e.g.*, one or more cationic lipids comprising from about 50 mol % to about 65 mol % of the total lipid present in the particle, provide ***unexpectedly superior advantages*** when used for the *in vitro* or *in vivo* delivery of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA)." '069 File History Jan. 31, 2011 at 9.

544. Ultimately, the examiner explained in the Notice of Allowance that the narrowed ranges of molar ratios was the sole basis for allowance: "The prior art of record is considered pertinent to applicant's disclosure. US 6,815,432, cited on an IDS discloses lipid formulations but

does not appear to disclose the ranges for each of the lipids recited in the instant claims." *See* '069 (Notice of Allowance) at 6. In other words, the Examiner accepted Applicant's arguments of unexpected results, which overcame the prior art rejections.

545. Moreover, Arbutus repeated this reliance on unexpected results during the IPR: "The '435 patent is directed to the surprising discovery that nucleic acid-lipid particles with ***high levels of cationic lipids*** and low levels of conjugated lipids exhibit favorable *in vivo* transfection efficiencies, as well as 'improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described.'" '435 Appeal, D.I. 67) at 19 (emphasis added). Arbutus further explained that this "surprising discovery" solved a long-felt need material to patentability: "The nucleic acid-lipid particle formulations of the '435 patent solved a long-felt need for compositions that could safely and effectively deliver nucleic acids to target cells of patients. Skilled artisans were skeptical that compositions ***having high levels of cationic lipid (i.e., 50 mol % to 85 mol %)*** and low levels of conjugated lipid (i.e., 0.5 mol % to 2 mol %) would be effective, let alone well-tolerated when administered *in vivo*. The combination of ***effectiveness*** and low toxicity that characterizes the claimed compositions surprised many in the field, and finally solved the delivery problem that hindered the field for decades." '435 IPR, PO Response at 2 (emphasis added). Additionally, Arbutus distinguished their alleged invention of "a nucleic acid-lipid particle comprised of relatively high levels of cationic lipids and low levels of conjugated lipids" from the prior art, which it argued taught that the cationic lipid components of lipid particles "should be minimized": "The claimed invention is a nucleic acid-lipid particle comprised of relatively high levels of cationic lipids and low levels of conjugated lipids. This combination was counterintuitive to the then-existing state of the art, as cationic lipids were known to be cytotoxic, systemically toxic, to

elicit an adverse complement-mediated immune response, and to cause particle aggregation that resulted in rapid clearance. *E.g.,* EX1007, 745 ("Minimizing the amount of cationic lipid is desirable . . . fewer, more highly charged molecules should mean a smaller metabolic effort. . .") EX1009, 5 ("the cationic lipid contributes significantly to the toxicity observed."); EX2016, 42 ("I wouldn't want anyone injecting cationic lipids into my bloodstream."). The prior art taught that the cationic lipid component of lipid particles should be minimized, regardless of whether used for *in vitro* or *in vivo* purposes. EX20231, ¶¶80-88." '069 IPR, PO Response at 29.

546. Based on Arbutus's statements in the specification of the Molar Ratio Patents and the intrinsic record (including the file history and the *Inter Partes* Reviews), the function of the claimed higher levels (i.e. ≥50 mol %) cationic lipid ranges is to form particles with increased membrane fluidity to safely and effectively deliver a therapeutic nucleic acid (*e.g.,* an interfering RNA) to distal target cells.

(2) The Function of 48.0 mol% SM-102 in the v2 Formulation

547. The 48.0 mol % of SM-102 in the v2 Formulation functions by interacting with the mRNA to drive delivery and protein expression as well as impart biodegradability to the particles. In particular, Moderna's lower concentration of its proprietary SM-102 cationic lipid [redacted] *See* Section VIII.A.5. For the reasons explained above, 48.0 mol % SM-102 in the v2 Formulation functions differently than the ≥50 mol % cationic lipid claimed in the Molar Ratio Patents.

(B) Way (≥50 mol% Cationic Lipid Range Limitations)

548. In my opinion, the 50 mol % cationic lipid claimed in the Molar Ratio Patents function in a different way to the 48.0 mol % SM-102 in the v2 Formulation. By being present at

higher levels, the ≥50 mol % cationic lipids claimed in the Molar Ratio Patents functions to increase membrane fluidity due to alkyl chains with multiple sites of unsaturation. Meanwhile, by being present at lower levels, the 48.0 mol % SM-102 in the v2 Formulation functions [redacted].

(1) The Way of ≥50 mol% Cationic Lipid Range Limitations in the Asserted Claims

549. The Molar Ratio Patents define "cationic lipid" as follows:

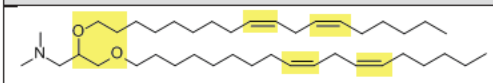
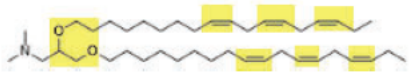
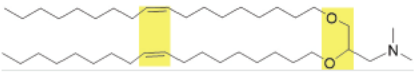
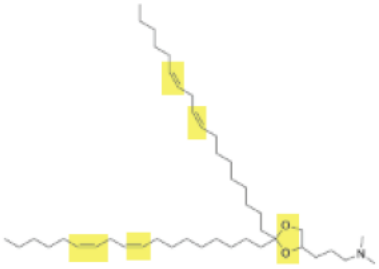
> The term 'cationic lipid' refers to any of a number of lipid species that carry a net positive charge at a selected pH. Such as physiological pH (e.g., pH of about 7.0). It has been surprisingly found that cationic lipids ***comprising alkyl chains with multiple sites of unsaturation, e.g., at least two or three sites of unsaturation, are particularly useful for forming lipid particles with increased membrane fluidity***. A number of cationic lipids and related analogs, which are also useful in the present invention, have been described in U.S. Patent Publication Nos. 20060083780 and 20060240554; U.S. Pat. Nos. 5,208,036; 5,264,618: 5,279,833; 5,283,185; 5,753,613; and 5,785,992; and PCT Publication No. WO96/10390, the disclosures of which are herein incorporated by reference in their entirety for all purposes. Non-limiting examples of cationic lipids are described in detail herein. In some cases, the cationic lipids comprise a protonatable tertiary amine (e.g., pH titratable) head group, C18 alkyl chains, ether linkages between the head group and alkyl chains, and 0 to 3 double bonds. Such lipids include, e.g., DSDMA, DLinDMA, DLenDMA, and DODMA.

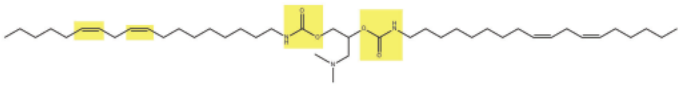
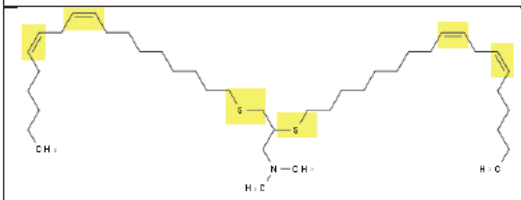
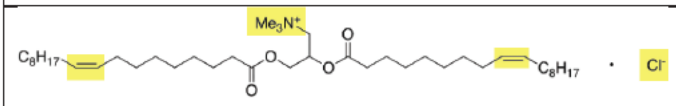
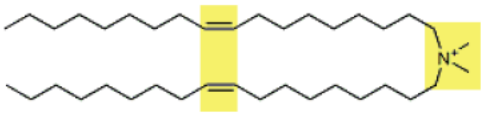
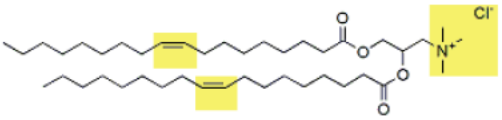
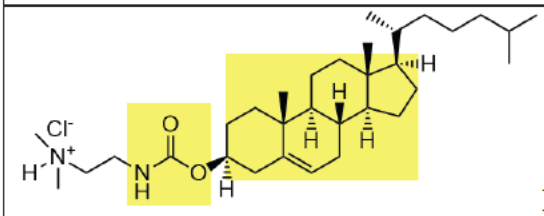
'069 Patent at 12:51-13:3 (emphasis added). Specifically, the Molar Ratio Patents explain that "[i]t has been surprisingly found that cationic lipids comprising alkyl chains with multiple sites of unsaturation, e.g., at least two or three sites of unsaturation, are particularly useful for forming lipid particles with increased membrane fluidity." '069 Patent at 12:53-57. In other words, the Molar Ratio Patents explain that "cationic lipids comprising alkyl chains with multiple sites of unsaturation" help to fuse the target cell to allow delivery of siRNA, thus identifying the way in which the ≥50 mol % cationic lipid functions.

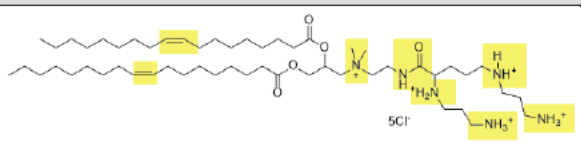
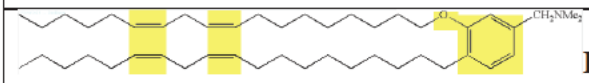
(1) The Way of 48.0 mol% SM-102 in the V2 Formulation

550. The ≥50 mol % cationic lipids disclosed in Molar Ratio Patents, such as DLinDMA, function in a different way from the 48.0 mol % SM-102 in the v2 Formulation. For example, unlike the lipids identified by the Molar Ratio Patents as being "particularly useful for forming lipid particles with increased membrane fluidity," '069 Patent at 12:53-57, SM-102 does not comprise alkyl chains with multiple sites of unsaturation. Indeed, SM-102 does not contain any unsaturation. As explained below, the way SM-102 drives delivery and biodegradability is with ester bonds.

551. There are other material differences between SM-102 and the specific cationic lipids disclosed in the Molar Ratio Patents. Examples of chemical features that are found in cationic lipids disclosed in the Molar Ratio Patents but not present in SM-102:

Cationic lipids disclosed in Molar Ratio Patents	Chemical features NOT present in SM-102
 **DLinDMA**	**Ethers; alkenes**
 **DLenDMA**	
 **DODMA**	
 **DLin-KC2-DMA**	
 **DLin-KC3-DMA**	

Cationic lipids disclosed in Molar Ratio Patents	Chemical features NOT present in SM-102
 DLin-KC4-DMA	
 DLin-C-DAP	Carbamoyl esters; alkenes
 DLin-S-DMA	Thioethers; alkenes
 DLin-TMA.Cl  DODAC  DOTMA	Quaternary ammonium salt; alkenes
 DC-Chol	Carbamoyl esters; sterol nucleus

Cationic lipids disclosed in Molar Ratio Patents	Chemical features NOT present in SM-102
 DOSPA	**Quaternary ammonium salt; polyamines; alkenes; amide**
 DMLBA	**Aryl ether, alkenes**

552. The CO-O functions in SM-102 are esters and not ethers, and a POSA would understand that esters and ethers are not chemically equivalent. The esters are the feature of the SM-102 that make it biodegradable and suitable for IM dosing, which is not taught by the Molar Ratio Patents, which focuses on alkyl chains with multiple sites of unsaturation. *See* Hassett 2019 at 2 ("The ionizable lipids screened here all contain a tertiary amine with ester-containing lipid tails to enable rapid *in vivo* metabolism."). Accordingly, the underlying mechanism of action for SM-102 is not equivalent to the mechanism for the cationic lipids disclosed in the Molar Ratio Patents. In fact, the ester linkages in the hydrophobic tails of Moderna's SM-102 lipid increase the rate of degradation of the lipid in the cytosol, and decrease the toxicity and immunogenicity of the LNP formulation.

553. Although MC3 is not disclosed in the Molar Ratio Patents (*see* Section IX.B.2) the evidence shows that Moderna's SM-102 lipid demonstrates improved attributes, including, for example, safety, efficiency, tolerability, and expression to existing cationic lipids, including MC3. *E.g.*, Benenato Dep. Tr. at 64:14-65:1, 72:5-11; MRNA-GEN-00508894 at 926-927; *see also* Benenato Dep. Ex. 8, MRNA-GEN-01062618, MRNA-GEN-00036907, MRNA-GEN-01625914, MRNA-GEN-00769265. Additionally, Genevant scientists themselves, including Kieu Lam and

Lorne Palmer, named inventors to the Molar Ratio Patents, acknowledged that SM-102 and MC3 are considerably more potent than DLinDMA. *E.g.*, GENV-00951182 at 182, 185.

554. Further, I note that the Molar Ratio Patents state "[i]t has been surprisingly found that cationic lipids comprising alkyl chains with multiple sites of unsaturation, e.g., at least two or three sites of unsaturation, are particularly useful for forming lipid particles with increased membrane fluidity." '069 patent at 12:53-58. In contrast, Moderna's SM-102 lipid has no unsaturation. A POSA would understand the role of unsaturation in the classes of lipids described in the Molar Ratio Patents to be the prevention of the crystallization of the lipid tails, thus "increase[ing] membrane fluidity."[45] In contrast to unsaturation to maintain membrane fluidity, Moderna's SM-102 has branched lipid tails conjugated from ester-linked precursors. This branching prevents crystallization and enhances fluidity, but it is the steric interference that increases fluidity, rather than unsaturation.

555. Further confirming that the "way" is different, Plaintiffs' documents[46] confirm that using lower levels of cationic lipid than claimed led to unfavorable results, whereas those same negative attributes are not applicable to the 48.0 mol % SM-102 used in the v2 Formulation. For example, the inventors found that lower levels of cationic lipid have a negative impact on activity, whereas higher amounts such as 57 mol % led to greater activity. GENV-00126198-348 at GENV-00126202, at 208; GENV-00063772, 73 at 78 (similar findings); GENV-00058026 at 032 (table Dr. Mitchell identified as underlying the Molar Ratio Patents, Table 2, shows lower cationic lipids

[45] Membrane fluidity describes the mobility of the outer membrane surface of an LNP. The fluidity is determined not only by the type of lipid tail of the ionizable lipid, but also by the amount of cholesterol and neutral lipid that is incorporated into the LNP, which partitions to the surface.

[46] To determine the function-way-result of the claim limitation, I considered the specification and the file history. I refer to Plaintiffs' documents here as they are consistent with my opinions based on the specification and file history.

performed poorer (with a higher IC-50) than Sample 9, the 1:57 formulation), at 034 (same, with respect to poor stability for lower cationic molar percentages, e.g. 53 mol %, compared to 57 mol % in the 1:57 embodiment), at 039 ("increasing the concentration of DLinDMA in formulation had strong positive effect on activity"). In fact, the inventors even noted that reducing cationic lipid DLinDMA in conjunction with an increase in PEG led to a strong negative effect. GENV-00126202, 214 (***"when DLinDMA (-)*** [i.e. reduced] and DPPC (+) - ***increasing PEG had a negative effect***"); *see also* GENV-00057731 (describing findings that high cationic lipid showed more rapid blood clearance, compared to low cationic lipid formulations which had slower blood clearance); GENV-00109171 ("the most potent formulation contains the highest mol% cationic lipid; reducing cationic lipid content by increasing cholesterol, DPPC, and PEG-C-DMA caused loss of activity"), at 82 ("reducing PEG-lipid concentration further may benefit activity"). During development of Moderna's COVID-19 Vaccine, by comparison, [redacted], which confirms that Moderna's cationic lipid at 48.0 mol % is acting in a different way to the cationic lipid at ≥50 mol % of the asserted claims. *See* Section VIII.A.4; *see also, e.g.* Parsons Dep. Ex. 40 at MRNA-GEN-00533662 [redacted].

(C) Result (≥50 mol% Cationic Lipid Range Limitations)

556. ≥50 mol % cationic lipid in the Asserted Claims of the Molar Ratio Patents achieve different results than 48.0 mol % cationic lipid. At a high level, the ≥50 mol % cationic lipids claimed in the Molar Ratio Patents efficiently delivers the siRNA payload to cells (e.g., tumor or distal targets such as the liver). Meanwhile, the 48.0 mol % SM-102 in the v2 Formulation achieves

the balance between efficient protein expression and biodegradability (i.e. the lipid is cleared quickly from the injection site) for intramuscular vaccine delivery, which as described above for the "way" was a result that the inventors were unable to achieve with the disclosed compositions and cationic lipids at 50mol% disclosed in the Molar Ratio Patents.

(1) The Result of ≥50 mol% Cationic Lipid Range Limitations in the Asserted Claims

557. The specification of the Molar Ratio Patents explains that there are distinct benefits of 50 mol % or more cationic lipid and that these distinct benefits were material to the patentability of the Molar Ratio Patents. Specifically, the specification explains:

> ***The present invention is based, in part, upon the surprising discovery that lipid particles comprising from about 50 mol % to about 85 mol % of a cationic lipid***, from about 13 mol % to about 49.5 mol % of a non-cationic lipid, and from about 0.5 mol % to about 2 mol % of a lipid conjugate ***provide advantages when used for the in vitro or in vivo delivery of an active agent, such as a therapeutic nucleic acid (e.g., an interfering RNA).*** In particular, as illustrated by the Examples herein, the present invention ***provides stable nucleic acid-lipid particles (SNALP) that advantageously impart increased activity of the encapsulated nucleic acid*** (e.g., an interfering RNA such as siRNA) and ***improved tolerability of the formulations in vivo***, resulting in a ***significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described***. Additionally, the SNALP of the invention are stable in circulation, e.g., resistant to degradation by nucleases in serum, and are substantially non-toxic to mammals such as humans. As a non-limiting example, FIG. 3 of Example 4 shows that one SNALP embodiment of the invention ("1:57SNALP) was more than 10 times as efficacious as compared to a nucleic acid-lipid particle previously described ("2:30 SNALP) in mediating target gene silencing at a 10-fold lower dose. Similarly, FIG. 2 of Example 3 shows that the "1:57 SNALP" formulation was substantially more effective at silencing the expression of a target gene as compared to nucleic acid-lipid particles previously described ("2:40 SNALP).
>
> In certain embodiments, the present invention provides improved compositions for the delivery of interfering RNA such as siRNA molecules. In particular, the Examples herein illustrate that the improved lipid particle formulations of the invention are highly effective in downregulating the mRNA and/or protein levels of target genes. Furthermore, the Examples herein illustrate that ***the presence of certain molar ratios of lipid components results in improved or enhanced activity of these lipid particle formulations of the present invention***. For instance, the "1:57 SNALP and "1:62 SNALP formulations described herein are exemplary formulations of the present invention that are particularly advantageous because

> they ***provide improved efficacy and tolerability in vivo***, are serum-stable, are substantially non-toxic, are capable of accessing extravascular sites, and are capable of reaching target cell populations.

'069 Patent at 5:44-6:19. (emphasis added). This passage of the specification confirms that the result of the use of higher levels of cationic lipid in the asserted claims is increased activity of the encapsulated siRNA, which are delivered intravenously to distal sites.

558. As explained above, the prosecution history of the Molar Ratio Patents further supports the distinct benefits of a lipid particle comprising 50 mol % or more cationic lipid. During prosecution of the '069 patent, the examiner explained: "It is clear from the specification that the present invention is based, in part, on the surprising discovery that 1:57 SNALP formulations provide new and unexpected results when used for the *in vitro* or *in vivo* delivery of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA). More particularly, Applicants have found that SNALP formulations having **increased** amounts of cationic lipid, *e.g.*, one or more cationic lipids comprising from about 50 mol % to about 65 mol % of the total lipid present in the particle, provide ***unexpectedly superior advantages*** when used for the *in vitro* or *in vivo* delivery of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA)." '069 File History Jan. 31, 2011 at 9.

559. Ultimately, the examiner explained in the Notice of Allowance that the narrowed ranges of molar ratios was the sole basis for allowance: "The prior art of record is considered pertinent to applicant's disclosure. US 6,815,432, cited on an IDS discloses lipid formulations but does not appear to disclose the ranges for each of the lipids recited in the instant claims." *See* '069 Notice of Allowance at 6.

560. Moreover, Arbutus repeated this disclaimer and reliance on unexpected results during IPR: "The '435 patent is directed to the surprising discovery that nucleic acid-lipid particles with ***high levels of cationic lipids*** and low levels of conjugated lipids exhibit favorable ***in vivo***

transfection efficiencies, as well as 'improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described.'" '435 Appeal, D.I. 67 at 19 (emphasis added). Arbutus further explained that this "surprising discovery" solved a long-felt need material to patentability: "The nucleic acid-lipid particle formulations of the '435 patent solved a long-felt need for compositions that could safely and effectively deliver nucleic acids to target cells of patients. Skilled artisans were skeptical that compositions having high levels of cationic lipid (i.e., 50 mol % to 85 mol %) and low levels of conjugated lipid (i.e., 0.5 mol % to 2 mol %) would be effective, let alone well-tolerated when administered *in vivo*. The combination of effectiveness and low toxicity that characterizes the claimed compositions surprised many in the field, and finally solved the delivery problem that hindered the field for decades." '435 IPR, PO Response at 2 (emphasis added). Additionally, Arbutus distinguished their alleged invention of "a nucleic acid-lipid particle comprised of relatively high levels of cationic lipids and low levels of conjugated lipids" from the prior art, which it argued taught that the cationic lipid components of lipid particles "should be minimized": "The claimed invention is a nucleic acid-lipid particle comprised of relatively high levels of cationic lipids and low levels of conjugated lipids. This combination was counterintuitive to the then-existing state of the art, as cationic lipids were known to be cytotoxic, systemically toxic, to elicit an adverse complement-mediated immune response, and to cause particle aggregation that resulted in rapid clearance. *E.g.,* EX1007, 745 ("Minimizing the amount of cationic lipid is desirable . . . fewer, more highly charged molecules should mean a smaller metabolic effort. . .") EX1009, 5 ("the cationic lipid contributes significantly to the toxicity observed."); EX2016, 42 ("I wouldn't want anyone injecting cationic lipids into my bloodstream."). The prior art taught that the cationic lipid component of lipid particles should be

minimized, regardless of whether used for *in vitro* or *in vivo* purposes. EX20231, ¶¶80-88." '069 IPR, PO Response at 29. This is consistent with my opinion that that nucleic acid-lipid particles comprising [≥50] mol% cationic lipid achieve different results than nucleic-acid lipid particles comprising <50 mol % cationic lipid.

(2) The Result of 48.0 mol% SM-102 in the v2 Formulation

561. The use of ≥50 mol % cationic lipids in the Asserted Claims achieve a different result as compared to 48.0 mol% SM-102 in the v2 Formulation.

562. For background, Dr. Kerry Benenato, a former Moderna scientist, invented a new cationic lipid called SM-102 for mRNA delivery that was ultimately used in Moderna's COVID-19 Vaccine. Benenato Dep. Tr. 74:7-76:14. Early in the evaluation of LNPs as a delivery system for mRNA vaccines, Moderna used MC3 as an ionizable lipid to deliver mRNA vaccines. Hassett 2019 at 6 ("MC3 formulated mRNA was the worst tolerated lipid tested whereas SM-102 was the best tolerated lipid tested."). [redacted]. MRNA-GEN-00018601 at -603. Ultimately, the evidence shows that SM-102 lipid degrades faster than MC3, due to the biodegradability of the SM lipids. MRNA-GEN-00480514 at Figure 8. MRNA-GEN00018601 at -603.

563. SM-102 was also selected as the amino lipid for IM delivery of LNPs for reasons including because it was the most potent lipid out of a panel of at least 30 ionizable lipids that were screened for expression and vaccine potency for the intramuscular (IM) route of administration in rodents. MRNA-GEN-00988589 at -591; MRNA-GEN-00480514; MRNA-GEN00018601 at -603; Hassett 2019 at 2; *see also* MRNA-GEN-00480514 at -514 ("1. Increases expression 3x over MC3 LNPs in NHP 2. Equal immunogenicity as MC3 LNPs in NHP 3. Minimal site of injection

reaction observed in NHP 4. Lowest pathology scores in the non-GLP rat tolerability study 5. Able to be formulated using a micro-tee 6. Stable up to 1 month stored in 20mM tris 8% sucrose at 0.2 mg/ml").

564. Moderna reported SM-102 having increased expression in NHPs and rodents as compared to MC3. MRNA-GEN-00480514 at -514, Figure 2 ("SM-102 and SM-107 were shown to exhibit 4-6x MC3 expression in mice."); MRNA-GEN-00480514 at -514, Figure 4 ("SM-102 had 3x the expression of MC3 LNPs."). Moderna also reported SM-102 as having increased immunogenicity in mice and similar immunogenicity as NHPs compared to MC3. MRNA-GEN-00480514 at -514, Figure 3 and 5 ("SM-102 and SM151 produced the highest titers in mice and SM-102, SM-140 and SM-151 LNPs had titers similar to MC3 in cynomolgus macaques."); 4 ("In NHPs, while three out of the five selected lipids yielded comparable expression to MC3-based LNPs, SM-102 lipid and Lipid M showed significantly more expression over time than MC3. For SM-102, the maximum antibody concentration measured 24 hours post injection was three times the antibody concentration measured with MC3 formulated material.").

565. In addition to SM-102 having higher expression and similar immunogenicity as MC3 in NHPs, Moderna reported SM-102 as having improved tolerability NHPs. MRNA-GEN-00988589 at -591. One of Moderna's goals was "to improve vaccine tolerability without affecting vaccine potency". Hassett 2019 at 2. Moderna reported in Hassett that, "increased innate immune stimulation driven by the LNP is not necessary for increased immunogenicity, illustrating that we have an opportunity to improve vaccine tolerability without affecting vaccine potency". Hassett 2019 at 2.

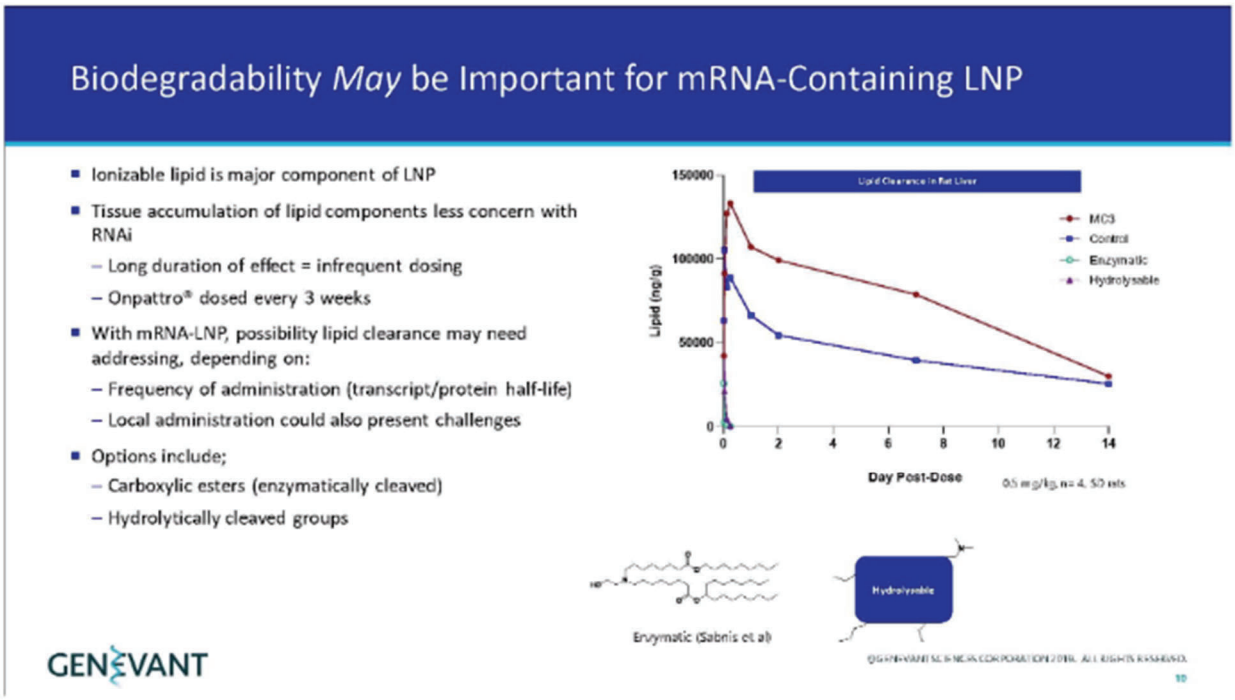
566. Moreover, NHPs in the MC3 group showed a stronger innate immune response compared to SM-102. Hassett 2019 at 5 ("NHPs in the MC3 group with the highest level of IL-6

also showed the highest level of edema, indicating a strong innate immune response in that individual animal."). NHPs in the MC3 group also have a stronger edema and erythema response compared to the SM-102 group after the first injection, and a stronger edema reaction compared to the SM-102 group after the second reaction. Hassett 2019 at 5; MRNA-GEN-00480514 at -514, Figure 7 and Figure 9.

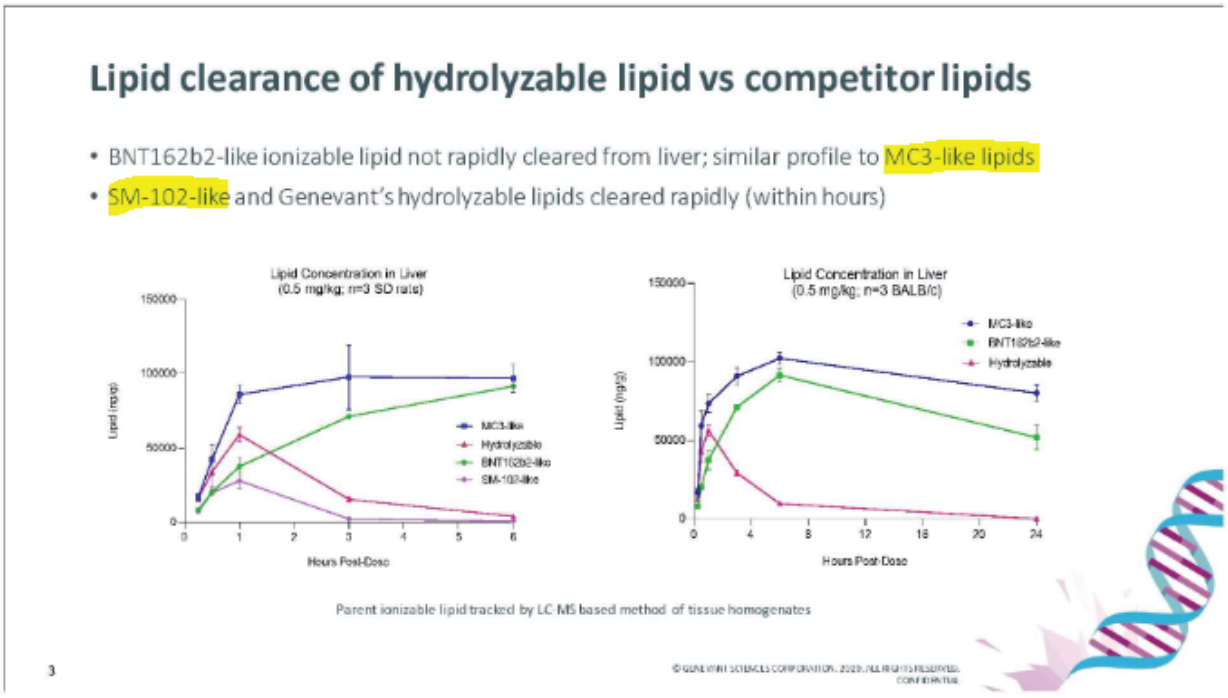
567. Furthermore, as reported in Hassett 2019, Moderna found that in Sprague-Dawley rats, "MC3-formulated mRNA was the worst tolerated lipid tested, whereas lipid H (SM-102) was the best tolerated lipid tested (Figures 5F-5I)". Hassett 2019 at 6. In addition, "with the exception of IP-10 at the 0.01 mg dose, lipid H (SM-102) induced the lowest systemic cytokine production." Hassett 2019 at 6.

568. As explained above, SM-102 exhibited improved tolerability in NHPs, rats and mice. SM-102's increased biodegradability over MC3 informed Moderna's hypothesis that SM-102 would exhibit increased tolerability as it would not remain at the injection site as long to elicit an immune response. Moreover, SM-102 also demonstrated similar immunogenicity as MC3. [redacted]. Hassett 4/26/2024 Tr. 68:20-69:1. Neither readout is solely indicative of vaccine efficacy.

569. Even Plaintiffs' documents acknowledge the significant difference that SM-102 and ionizable lipids made, including to potency and biodegradability. For example, a November 14, 2019 Genevant presentation titled "Strategies for the Delivery of Nucleic Acid Therapies" explains the importance of biodegradability for mRNA-Containing LNPs:



GENV-00285086 at 93-95. The presentation noted that "tissue accumulation of lipid components less concern with RNAi" and that "local administration could also present challenges" for mRNA-LNP; *see also* GENV-00286019 (presentation titled "Genevant's Biodegradable LNP Platform"); GENV-00286884 (presentation titled "Biodegradable LNP"). Further, a May 11, 2021 Genevant presentation titled "Biodegradable LNP Platform" illustrates the advantages of "SM-10-like" lipids over "MC3-like lipids" with respect to lipid clearance:



GENV-00303059 at GENV-00303061 (annotated). This is consistent with my opinion that the way that 48.0 mol% SM-102 functions in the v2 Formulation is not equivalent to the way that the ≥50 mol % cationic lipid claimed in the Molar Ratio Patents functions.

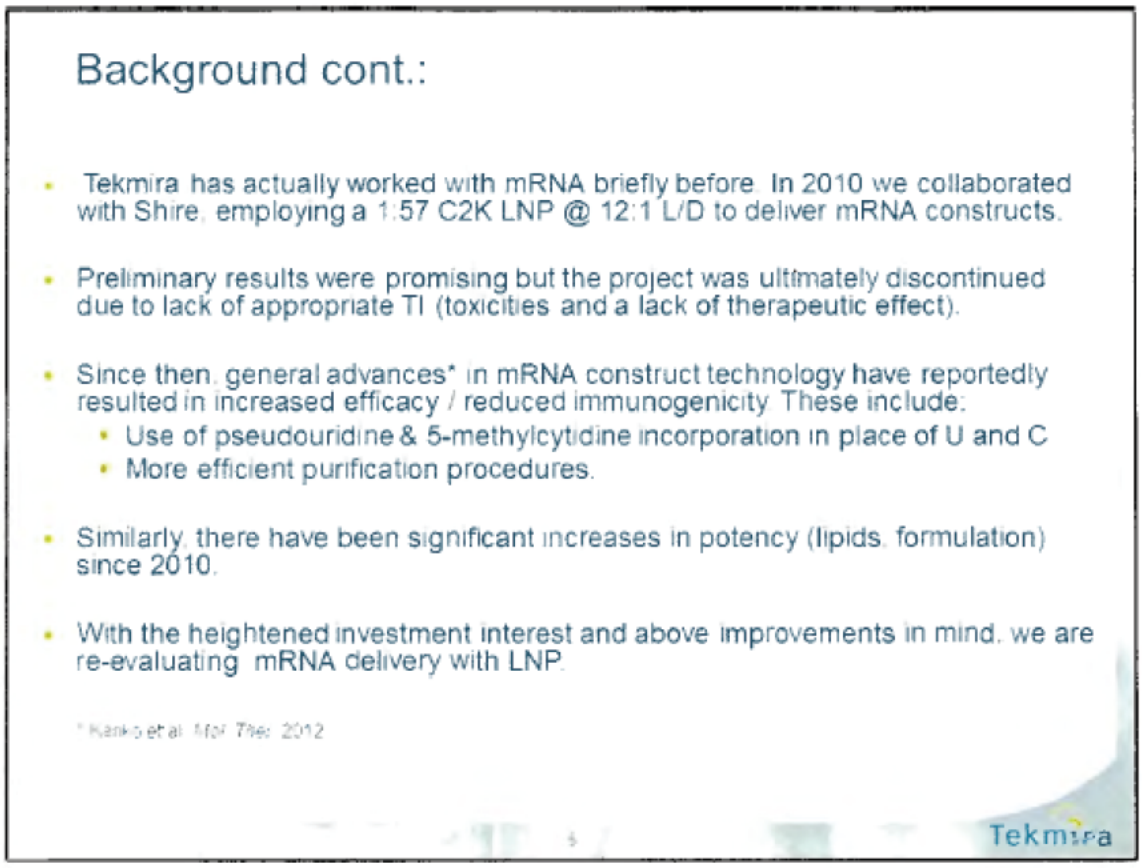
570. For example, the evidence shows that Moderna's lower concentration of its proprietary SM-102 cationic lipid (i.e. under 50 mol%) achieves improved tolerability for intramuscular doses and improved local protein expression. *See* Hassett 2019 at 6 ("MC3 formulated mRNA was the worst tolerated lipid tested whereas [SM-102] was the best tolerated lipid tested."); at 2 ("Many of our novel biodegradable lipids proved superior to MC3 for both protein expression and immunogenicity upon IM administration.'); at 8 ("The histopathology presented here for [SM-102], compared to that for MC3, is consistent with improved tolerability and reduced innate immune stimulation. The reduction in inflammatory cell infiltrate, myofiber damage, and systemic cytokines support the hypothesis that mRNA vaccines may not require a strong adjuvant response for potent immune responses."). Local protein expression is important

because the Accused Product is delivered intramuscularly, unlike the Molar Ratio Patents which are directed intravenous delivery. *See* MRNA-GEN-00018512 (Section 3.2.P.2 of the BLA titled "Pharmaceutical Development") at MRNA-GEN-00018513-4. Indeed, Moderna explained the importance of delivery mechanism to lipid selection:

> SM-102 is the ionizable lipid component of the SM-102 LNP. Under the acidic conditions of the encapsulation reaction, SM-102 provides a net positive charge to the LNP, which drives the spontaneous encapsulation of the negatively charged mRNA through electrostatic attraction. The concentration of SM-102 in the LNP was chosen to provide a stoichiometric excess of cationic charge and enable full charge complexation of the mRNA and efficient encapsulation.
>
> SM-102 is a biodegradable lipid. It was identified and developed through a screening process that examined the impact of a range of biodegradable lipids for protein expression and immunogenicity when injected by the intramuscular route. SM-102 was selected as the most potent lipid out of a panel of 30 ionizable lipids that were screened for expression and vaccine potency via the intramuscular (IM) route of administration in rodents. Finally, SM-102 was selected as the lead ionizable lipid due to improved tolerability over the lipids that were evaluated in non-human primates.

MRNA-GEN-00018512 (Section 3.2.P.2 of the BLA titled "Pharmaceutical Development") at MRNA-GEN-00018513-4.

571. In contrast, Plaintiffs' documents show that when they tried their own LNP with mRNA, they could not get an appropriate therapeutic index and had issues with toxicity such that their efforts were "ultimately discontinued":



Heyes Dep. Ex. 8 at 5. This is consistent with my opinion that the results achieved by 48.0 mol% SM-102 in Moderna's v2 Formulation are not equivalent to the results achieved by the cationic lipid mol % claimed in the Molar Ratio Patents.

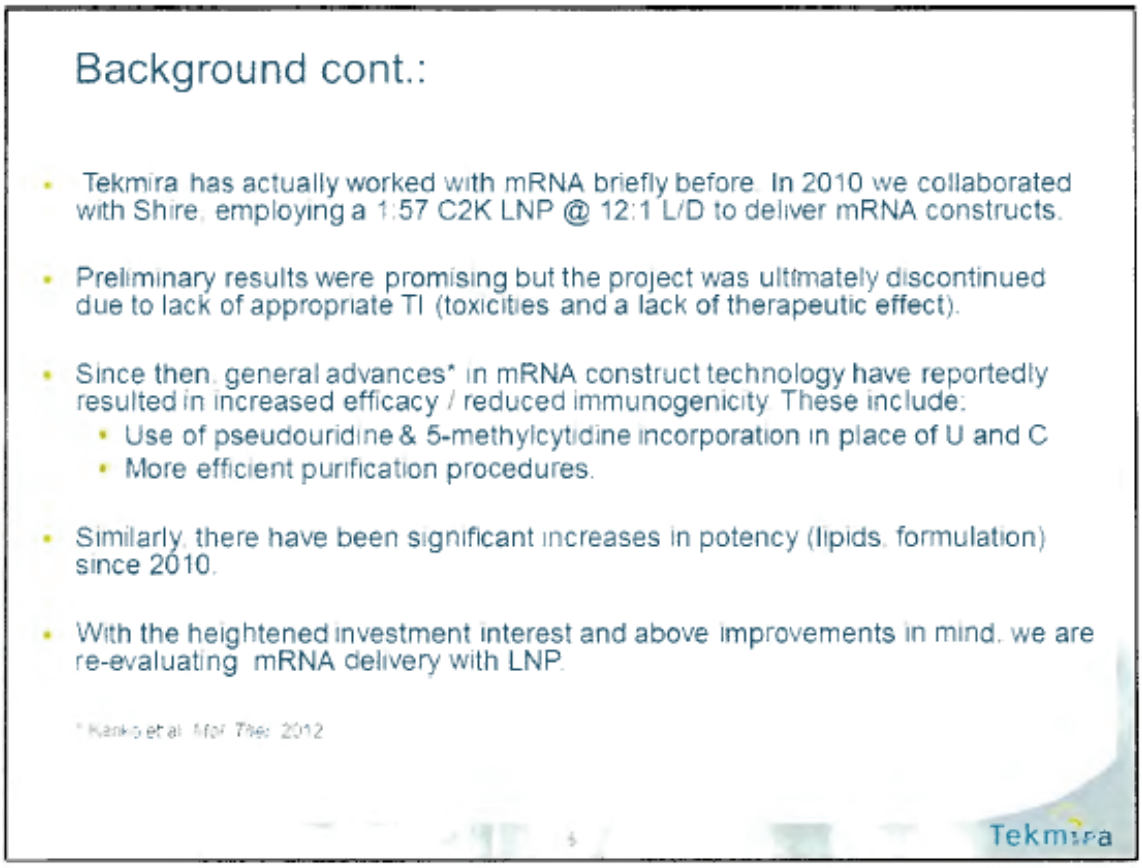
iii. Substantial Differences (≥50 mol% Cationic Lipid Range Limitations)

572. In my opinion, the physical and chemical properties of 48.0 mol % SM-102 cationic lipid in Moderna's SPIKEVAX® v2 Formulation are substantially different from the physical and chemical properties of the claimed ≥50 mol% cationic lipid ranges. This is consistent with the conclusions of my above analysis in terms of function, way, and result, which I incorporate by reference.

573. The substantial differences is explained by the specific mol % concentration of cationic lipid. For example, SM-102 does not comprise "alkyl chains with multiple sites of

unsaturation," which the Molar Ratio Patents explain are "useful for forming lipid particles with increased membrane fluidity." '069 Patent at 12:53-57. And the evidence shows that Moderna's SM-102 achieves improved tolerability for intramuscular doses and improved local protein expression as compared to MC3. *See* Hassett 2019 at 6 ("MC3 formulated mRNA was the worst tolerated lipid tested whereas [SM-102] was the best tolerated lipid tested."); at 2 ("Many of our novel biodegradable lipids proved superior to MC3 for both protein expression and immunogenicity upon IM administration."); at 8 ("The histopathology presented here for [SM-102], compared to that for MC3, is consistent with improved tolerability and reduced innate immune stimulation. The reduction in inflammatory cell infiltrate, myofiber damage, and systemic cytokines support the hypothesis that mRNA vaccines may not require a strong adjuvant response for potent immune responses."). Moreover, these differences are important because Moderna's SPIKEVAX® delivers mRNA intramuscularly, unlike the Molar Ratio Patents which are directed to intravenous delivery of siRNA. Indeed, Plaintiffs' documents show that when they tried their

own LNP with mRNA, they could not get a therapeutic index and had issues with toxicity.



Heyes Dep. Ex. 8 at 5.

574. Additionally, Dr. Mitchell does not acknowledge that in his opinion, the v2 formulation infringes under the doctrine of equivalents despite not meeting up to two distinct claim elements literally: limitations of the '435 Patent claims requiring less than 49.5 mol% non-cationic lipid, and the limitations of '435, '069, '668 and '359 claims requiring more than 50 mol% cationic lipid. The fact that Moderna's v2 formulation does not literally meet multiple independent and distinct limitations in these asserted claims further supports my opinion that the differences are far more than substantial.

575. In sum, the evidence that I discuss above in the function/way/result framework shows that the 48.0 mol % SM-102 cationic lipid concentration in Moderna's SPIKEVAX® v2

Formulation is substantially different from claimed cationic lipids and lipid ranges in the Molar Ratio Patents with respect to their physical and chemical properties. Additionally, the fact that Moderna's v2 formulation does not literally meet up to three independent and distinct limitations further supports my opinion that the differences are far more than substantial.

iv. Prosecution History Estoppel (≥50 mol% Cationic Lipid Range Limitations)

576. In my opinion, prosecution history estoppel precludes Plaintiffs' arguments that Moderna's v2 Formulation infringes all Asserted Claims of the '069, '359, '668, and '435 patents requiring "from 50 mol % to 65 mol %" or "from 50 mol % to 85 mol %" of a cationic lipid (including dependent claims reciting narrower ranges) under the doctrine of equivalents based on narrowing claim amendments and based on arguments during prosecution that would lead a competitor to rely on disclaimers of claim scope by the applicant of cationic lipids less than 50 mol% cationic lipid.

577. In my opinion, the applicant amended their patent claims to be narrower and did so for the purpose of patentability. During prosecution of the '069 patent, the examiner rejected the claims as being anticipated by MacLachlan, et al. (US 2006/0008910), which "teaches the SNALP wherein the cationic lipid is from about 2 mol % to about 60 mol % of the total lipid present in the particle (paragraph 85), the phospholipid is from about 5% to about 90% or from about 10% to about 85% of the total lipid present in the particle (paragraph 85), the cholesterol is from about 20% to about 55% of the total lipid present in the particle (paragraph 85, top of page 8), and the conjugated lipid is from about 1 % to about 20% of the total lipid present in the particle (paragraph 85)." '069 File History May 12, 2011 at 2-4. The examiner tied the rejection to the inclusion of "about" in the claims explaining:

> The claims are further directed to the particle wherein the nucleic acid is a siRNA, the relative amounts of components read on a broad range of amounts because of

> the term 'comprising about'. The applicants do not provide a definition of the term in the specification. Thus, 'comprising about' could embrace an amount+/- 10, 20, 30 mol % of a lipid component.

'069 File History May 12, 2011 at 2. The examiner further provided a comparison of the lipid components in the application and MacLachlan:

Application	MacLachlan
instant claims of '367 1) cationic lipid comprising from about 50-65 mol % 2) phospholipid comprises from about 4-10 mol % 3) cholesterol comprising from about 30-40 mol% 4) conjugated lipid comprising from about 0.5-2 mol%	pre-grant US publication (paragraph 0085) 1) cationic lipid 2-60, 5-50, 10-45, 20-40, 30 mol% 2) phospholipid 5-90 mol% 3) cholesterol 20-55 mol % 4) conjugated lipid 1-20 mol %

'069 File History May 12, 2011 at 3-4. The examiner further rejected pending claims as obvious in view of Maclachlan, et al. (US 2006/0008910) and further in view of Fosnaugh, et al. (US 2003/0143732). '069 File History May 12, 2011 at 5-6. The examiner explained:

> In response to applicant's argument that Fosnaugh and Maclachlan do not teach or suggest 1:57 SNALP formulation and their new and unexpected results, the argument is not found persuasive because while it is acknowledged that 1 :57 shows a new an unexpected result, the product recited in ***the instant claims read on broad range of SNALP formulations***, including 2:30 and 2:40 ***because of the term 'comprising from about'***. The term is broad because the specification does not provide a definition of the term and the term could read on SNALP formulations other than 1:57, e.g., 2:30 and 2:40.

'069 File History May 12, 2011 at 6 (emphasis added). The examiner further rejected pending claims as invalid for obviousness-type double patenting over reference claims that recited overlapping ranges. '069 File History May 12, 2011 at 7-14. After examiner interviews, the applicant amended the claims to remove "about":

1. (Currently amended) A nucleic acid-lipid particle comprising:

(a) a nucleic acid;

(b) a cationic lipid comprising from ~~about~~ 50 mol % to ~~about~~ 65 mol % of the total lipid present in the particle;

(c) a non-cationic lipid comprising a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the phospholipid comprises from ~~about~~ 4 mol % to ~~about~~ 10 mol % of the total lipid present in the particle and the cholesterol or derivative thereof comprises from ~~about~~ 30 mol % to ~~about~~ 40 mol % of the total lipid present in the particle; and

(d) a conjugated lipid that inhibits aggregation of particles comprising from ~~about~~ 0.5 mol % to ~~about~~ 2 mol % of the total lipid present in the particle.

'069 File History Aug. 11, 2011 at 2. The applicant explained:

> During the interview, Applicants' representatives proposed amending the claims to delete the word 'about' from the ranges of lipid components and argued that the claimed ranges were not anticipated by MacLachlan *et al.* (US2006/0008910) because that reference failed to disclose the claimed ranges with sufficient specificity as required by M.P.E.P 2131.03 (II) and *Atofina*.

'069 File History Aug. 11, 2011 at 6. The applicant argued:

> In making both rejections, the Examiner alleges that the term 'comprising from about' recited in the instant claims embraces a broad range of lipid components. In an earnest effort to expedite prosecution, but without acquiescing on the merits of the rejection, Applicants have amended the claims to delete 'about' from the ranges of lipid components recited therein.

'069 File History Aug. 11, 2011 at 7. The applicant further provided a comparison of the ranges of lipid components in the amended claims and MacLachlan:

Lipid Component	Claim 1 as Amended	US 2006/0008910*
Cationic Lipid	50-65 mol %	"2-60, 5-50, 10-45, 20-40, 30 mol%"
Phospholipid	4-10 mol %	"5-90 mol%"
Cholesterol	30-40 mol %	"20-55 mol %"
Conjugated Lipid	0.5-2 mol %	"1-20 mol %"

*The ranges set forth in this column are reproduced from page 4 of the Office Action mailed May 12, 2011.

'069 File History Aug. 11, 2011 at 8. The applicant did not provide another definition of "about" when responding to the Examiner. I understand that Plaintiffs argued, and the Court accepted, that "about" in the context of the intrinsic record means "+/- 10, 20, 30 mol % of a lipid component." *See* D.I. 266 (Memorandum Opinion re Claim Construction) at n. 7; *see also* Plaintiffs' Markman Presentation at slides 31–36.

578. Further, during prosecution of the '069 patent, the examiner explained:

> It is clear from the specification that the present invention is based, in part, on the surprising discovery that 1:57 SNALP formulations provide new and unexpected results when used for the *in vitro* or *in vivo* delivery of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA). More particularly, Applicants have found that SNALP formulations having **increased** amounts of cationic lipid, *e.g.*, one or more cationic lipids comprising from about 50 mol % to about 65 mol % of the total lipid present in the particle, provide ***unexpectedly superior advantages*** when used for the *in vitro* or *in vivo* delivery of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA).

'069 File History Jan. 31, 2011 at 9; *see also* '069 File History Jan. 31, 2011 at 6–12 (arguing the amendments overcame other rejections including obviousness-type double patenting).

579. Ultimately, the examiner explained in the Notice of Allowance that the narrowed ranges of molar ratios was the sole basis for allowance: "The prior art of record is considered pertinent to applicant's disclosure. US 6,815,432, cited on an IDS discloses lipid formulations but does not appear to disclose the ranges for each of the lipids recited in the instant claims." *See* '069 Notice of Allowance at 6. A POSA would understand from this that the arguments and amendment deleting the word "about" were made to overcome rejections from the Examiner, including prior-art rejections, and that the arguments and amendments were successful in getting the claims allowed by the Examiner (in other words, those amendments and arguments were clearly made for purposes of patentability).

580. Similarly, the applicant amended their patent claims of the '359, '668, and '435 patents to be narrower and did so for the purpose of patentability. Plaintiffs are estopped from

asserting the doctrine of equivalents to capture less than 50 mol % of a cationic lipid for the '359, '668, and '435 patents because during prosecution of the '359 and '668 patents, the applicants filed preliminary amendments to delete "about" from original claims reciting "a cationic lipid comprising from about 50 mol % to about 65 mol % of the total lipid." *See, e.g.,* '359 File History Oct. 5, 2011 at 114, Amdt. Dated Mar. 28, 2012 at 4; '668 File History Jun. 26, 2013 at 114, Nov. 6, 2013 at 5. And during prosecution of the '435 patent, the applicants filed preliminary amendments to delete "about" from original claims reciting "a cationic lipid comprising from about 50 mol % to about 85 mol % of the total lipid." *See, e.g.,* '435 File History Aug. 18, 2014 at 114, Feb. 26, 2015 at 2. Without these amendments, applicant would have known from the earlier '069 prosecution that the claims would face rejection again over the prior art, confirming the amendments were made for patentability. Plaintiffs are also estopped from arguing Moderna's v2 Formulation infringes any Asserted Claims of the '359, '668, and '435 patents requiring from 50 mol % to 65 or 85 mol % of a cationic lipid under the doctrine of equivalents because the '359, '668, and '435 patents are issued from continuation applications of the '069 patent and use the same claim terms as in the '069 patent (reciting cationic lipid amounts in mol % ranges), which lack the word "about," which a POSA would understand would carry the same meaning. At no point during prosecution of the later '359, '668, and '435 patents did the applicant inform the Examiner that the disclaimer was withdrawn, and that the pending claims in those later patent applications needed to be examined again in light of the prior art such as MacLachlan.

581. I understand that when surrendering claim scope for reasons related to patentability, as the applicant did here, there is a presumption that applicant has surrendered everything between the original claim limitation and the amended claim limitation. The applicant never responded to the examiner to state that it intended to disclaim any amount less than +/-30% variability.

Therefore, when the applicant disclaimed "about" (which examiner defined as +/-10/20/30%), it disclaimed every variation leading up to that (*e.g.*, +/- 0.00001% to +/-30). I further understand that the Court has already found that by removing the word "about," the applicant disclaimed variability of "+/- 10, 20, 30 mol %" from the claims. D.I. 266 (Memorandum Opinion re Claim Construction) at 21 ("a claimed range of 'about' 50–65 mol % could potentially encompass a range as small as 40–75 mol % and as large as 20–95 mol %.[7] When Plaintiff removed the phrase 'comprising about,' it only ***clearly disclaimed these broader ranges*** and not the scientific conventions of rounding") (emphasis added).

582. Based on the Examiner's definition of "about", which the applicant accepted, the claims before and after the amendment are as follows:[47]

	Original claim 1 as of 1/31/2011	**Amended claim**	**Scope of surrendered territory**	**v2 Formulation**
Cationic Lipid	About 50 mol % to about 65 mol % (20 to 95 mol %)	50 mol % to 65 mol %	<50 mol % and 65 to 95 mol %	48.0 mol %
Phospholipid	About 4 mol % to about 10 mol % (0.0 to 40 mol %)	4 mol % to 10 mol %	<4 mol % and 10 to 40 mol %	11.0 mol %
Cholesterol	About 30 mol % to about 40 mol % (0.0 to 70 mol %	30 mol % to 40 mol %	<30 mol % and 40 to 70 mol %	38.5 mol %
Conjugated lipid	About 0.5 to about 2 mol% (0.0 to 32 mol %)	0.5 mol % to 2 mol %	>2 to 32 mol%	2.5 mol %

[47] As noted above at ¶ 312, throughout this section I do not explicitly refer to rounding for simplicity, but I do apply the Court's claim construction.

As shown above, Moderna's v2 Formulation has a 48.0 mol % cationic lipid, which falls within the scope of the surrendered territory. Although I show the '069 claims above as an example, the same analysis applies for the related '435, '668, '359 patents.

583. In my opinion, a nucleic acid-lipid particle comprising 48 mol % cationic lipid (or any amount between 45 mol % and 50 mol %) was foreseeable to a POSA at the time the applicant made their narrowing amendment. As demonstrated in the file history, the prior art disclosed incremental percentages of lipid components in nucleic acid-lipid particles. *See, e.g.*, '069 File History May 12, 2011 at 3-4 (summarizing disclosures of MacLachlan, U.S. 2006/0008910); '069 File History Aug. 11, 2011 at 8 (same). During prosecution, the examiner also explained:

> In response to applicant's argument that Fosnaugh and Maclachlan do not teach or suggest 1:57 SNALP formulation and their new and unexpected results, the argument is not found persuasive because while it is acknowledged that 1 :57 shows a new an unexpected result, the product recited in ***the instant claims read on broad range of SNALP formulations***, including 2:30 and 2:40 ***because of the term 'comprising from about'***. The term is broad because the specification does not provide a definition of the term and the term could read on SNALP formulations other than 1:57, e.g., 2:30 and 2:40.

'069 File History May 12, 2011 at 6 (emphasis added). This explanation further supports estoppel because it shows that the equivalents were foreseeable. In other words, the applicant already had an earlier patent to the 2:40 formulation with overlapping ranges, as raised by the examiner, showing that the applicant knew that other ranges existed, such as 48 mol % cationic lipid, and chose to disclaim it. Likewise, the specification of the '069 Patent was drafted with incremental percentages, showing the ability to describe incremental variation in lipid mol %. *See, e.g.*, '069 Patent at 18:40–19:2.

584. Additionally, based on my review of the file histories, the applicant's reasons for the claim amendments were not tangential to the alleged equivalent (i.e., nucleic acid-lipid particles comprising <50 mol % cationic lipid). As I described above, these claim amendments to

remove "about" were made to overcome rejections of the prior art that taught overlapping ranges of mol % cationic lipid, and specifically an embodiment comprising about 40 mol% cationic lipid referred to as the "2:40" formulation. Nor do I see another reason that would have prevented Plaintiffs from describing and claiming nucleic acid-lipid particles comprising lower mole percentages of cationic lipid. As I described above, nucleic acid-lipid particles comprising varying amounts and ranges of cationic lipid were routinely described in the prior art and Plaintiffs were capable of doing so in the specification. When the applicant wanted to seek claims to lipid particles with lower amounts of cationic lipid, they were clearly able to do so. *See* '378 Patent Claim 1 (with no lower limit on the cationic lipid).

585. Reviewing the arguments the applicant made about the alleged unexpected results of nucleic acid-lipid particles comprising greater than 50 mol % cationic lipid as well as the arguments made when amending the claim described above, as well as emphasizing the narrowness of the claims compared to the prior art overlapping ranges, a competitor would reasonably believe that Plaintiffs were effectively surrendering and disclaiming nucleic acid-lipid particles comprising less than 50 mol % cationic lipid.

586. Further supporting the argument-based estoppel, Plaintiffs also argued to the Patent Office that the alleged unexpected results and purported innovative aspects of the invention arising from "high levels of cationic lipids" to try to distinguish prior art. For example, during the '069 patent IPR, Plaintiffs alleged:

> The '069 patent Is directed to the ***surprising discovery that nucleic acid-lipid particle formulations with high levels of cationic lipids and low levels of conjugated lipids*** exhibit favorable in vivo transfection efficiencies as well as "improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index [a measure of dosage relative to toxic effect] as compared to nucleic acid-lipid particle compositions previously described." . . . ***Reflecting this discovery, the '069 patent claims nucleic acid-lipid particle formulations with high levels of cationic lipids (50–65 mol %) and low levels of conjugated lipids***

> ***(0.5–2 mol %)***—as well as specific levels of cholesterol/derivative (30-40 mol %) and phospholipid (4-10 mol %).

See, e.g., IPR2019-00554, Paper 7 (Patent Owner's Preliminary Response) at 13, 14, 34, 45–46 (emphasis added); id., Paper 15 (Patent Owner's Response) at 7, 8, 29–30, 32, 62, 64. During the IPR for the '435 patent, Plaintiffs again alleged:

> The '435 patent discloses the ***"surprising discovery" that nucleic acid-lipid particle formulations with a high level of cationic lipid and a remarkably low level of conjugated lipid*** exhibited favorable in vivo transfection efficiencies as well as "improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index [a measure of dosage relative to toxic effect] as compared to nucleic acid-lipid particle compositions previously described." . . . ***Reflective of this discovery, the '435 patent claims nucleic acid-lipid particle formulations with a high level of cationic lipid (50–85 mol %) and an unconventionally low level of conjugated lipid (0.5–2 mol %).***

See, e.g., IPR2018-00739, Paper 12 (Patent Owner's Preliminary Response) at 2, 6–8, 12, 24, 26, 37 (emphasis added); id., Paper 24 (Patent Owner's Response) at 2, 14, 19–21, 24, 32, 47, 54–55. These statements would also apply to the '359 and '668 patents, which are in the same patent family and likewise claim "high levels of cationic lipids (50–65 mol %)." From these arguments, a competitor would reasonably believe that Plaintiffs were effectively surrendering and disclaiming nucleic acid-lipid particles comprising less than 50 mol % cationic lipid. It is my understanding that these arguments preclude Plaintiffs from now recapturing nucleic acid-lipid particles claimed with less than 50 mol % cationic lipid under the '069, '435, '359 and '668 patents.

v. Public Dedication

587. Plaintiffs are precluded from asserting that any Asserted Claims of the '069, '359, '668, and '435 patents cover the v2 Formulation under the doctrine of equivalents because the specification of the patents discloses the unclaimed subject matter such that it has been dedicated to the public. For example, the '069 patent specification discloses embodiments with cationic lipid comprising ranges of "about 50 mol %" or more of the total lipid:

> In some embodiments, the cationic lipid may comprise from ***about*** 50 mol % to about 90 mol %, from about 50 mol % to about 85 mol %, from about 50 mol % to about 80 mol %, from about 50 mol % to about 75 mol %, from about 50 mol % to about 70 mol %, from about 50 mol % to about 65 mol %, or from about 50 mol % to about 60 mol % of the total lipid present in the particle.

See, e.g., '069 patent at 18:40–46 (emphasis added).[48] As detailed above, during prosecution of the '069 patent, the examiner defined "about" as "+/-***20, 30 mol % of a lipid component***." '069 File History May 12, 2011 at 2. The above passage in the specification would therefore be understood to refer to embodiments with 20 mol % to 100 mol % cationic lipid. Additionally, during the claim construction phase of this case, I understand that Plaintiffs relied on the specification containing "embodiments [that] comprise less than 50 mol % cationic lipid. Plaintiffs' Markman Presentation at slides 84 and 104–105 (citing '378 Patent at 20:19-34, 52:59-63). The specification discloses embodiments with 45–50 mol % cationic lipid, which is the scope of equivalence Plaintiffs now seek to capture through the doctrine of equivalents. Because these were disclosed in the specification but not claimed in the '069, '359, '668, and '435 patents, in my opinion a POSA would understand that the applicant dedicated such embodiments to the public.

588. My opinion that the applicant surrendered this claim scope is also supported by applicant's statements in the specification and the file history distinguishing the present invention from the prior art 2:40 formulation, which was described as inferior. *See, e.g.*, '069 patent at 5:66–6:3 ("FIG. 2 of Example 3 shows that the "1:57 SNALP" formulation was substantially more effective at silencing the expression of a target gene as compared to nucleic acid-lipid particles previously described ("2:40 SNALP")."); '069 File History Jan. 31, 2011 at 10 (similar); '069 File History Aug. 11, 2011 at 9–10 (similar). Moderna's LNP with 48.0 mol % cationic lipid is far

[48] The '069, '359, '668, and '435 patents are in the same family and share the same specification.

closer to the 40 mol% cationic lipid in the supposedly inferior prior art 2:40 formulation than the 1:57 embodiment in the Molar Ratio Patents, which contains 57 mol% cationic lipid.

589. My opinions are reinforced by the later '378 Patent, in which Plaintiffs obtained a patent with no lower limit on the cationic lipid, thus covering the embodiments it chose ***not*** to claim in the earlier family members (i.e. '069, '359, '668, and '435 patents).

590. Because the issued '069, '359, '668, and '435 patents claim a nucleic acid-lipid particle comprising a cationic lipid comprising "from 50 mol % to 65 mol %" or "from 50 mol % to 85 mol %" of the total lipid in the particle, while the specification discloses from >20 mol % cationic lipid, Plaintiffs are estopped from enforcing any unclaimed embodiments comprising 20 to 50 mol % of a cationic lipid, as that scope has been dedicated to the public.

vi. Vitiation

591. I understand a claim term is vitiated when the proposed equivalent embraces a structure that is specifically excluded from the scope of the claims. As explained above, the applicant disclaimed embodiments comprising less than 50 mol % of a cationic lipid and the examiner explained in the Notice of Allowance for the '069 patent that the narrowed ranges of molar ratios was the sole basis for allowance:

> The prior art of record is considered pertinent to applicant's disclosure. US 6,815,432, cited on an IDS discloses lipid formulations but does not appear to disclose the ranges for each of the lipids recited in the instant claims.

'069 Notice of Allowance at 6. Vitiating the numerical limitations requiring a cationic lipid at specified mol % ranges, as would be required under Plaintiffs' theories of infringement under the doctrine of equivalents, would deprive the public of the notice function of the claims and thereby render the claims meaningless. I incorporate my function-way-result analysis above, which further supports my opinion. Thus, in my opinion, Plaintiffs are precluded from claiming that that

Moderna's v2 Formulation infringes any Asserted Claims of the '069, '359, '668, and '435 patents under the doctrine of equivalents.

592. I note that Dr. Mitchell does not explain why prosecution history estoppel, vitiation, and/or public dedication should not apply in this instance. To the extent Dr. Mitchell does so later, I reserve the right to respond.

d. No Infringement of Conjugated Lipid / PEG Range Limitations Under Doctrine of Equivalents

593. In my opinion, the PEG-DMG-2000 lipids and the specific mol % therefore in Moderna's SPIKEVAX® v2 Formulation have different functions, ways, and results, and are substantially different from the claimed lipids and lipid molar ratios claimed in the Molar Ratio Patents. I incorporate by reference Section X.D.4.c above.

594. For the reasons explained in Sections X.D.1 and X.D.3.a, under Plaintiffs' view of the claims and Plaintiffs' new infringement theory that focuses on the lipid content of individual lipid particles, the Certificates of Analysis do not provide evidence of the lipid content of any individual particle, and do not show that the particles meet Plaintiffs' hypothetical claims.

i. Dr. Mitchell's Function-Way-Result Analysis

(A) Function (<2mol% Conjugated Lipid / PEG Range Limitations).

595. Dr. Mitchell again conflates equivalence of the function of the conjugated lipid/ PEG broadly with the function of the specific claimed conjugated lipid/ PEG mol %. While I do not disagree with Dr. Mitchell that a "function of the conjugated lipid in the claimed non-cationic lipid mol % limitation is to promote particle stability (*e.g.*, via decreasing the aggregation of particles), which can impact fusogenicity and circulation time," Mitchell Rep. ¶ 712, I disagree with Dr. Mitchell's conclusion that "the conjugated lipid mol % of lots of Moderna's COVID-19 vaccine drug product formulated using the target v2 Formulation (including specifically its 2.5

mol % target for the PEG2000-DMG conjugated lipid), is insubstantially different from the claimed conjugated lipid mol % limitations . . . .” Mitchell Rep. ¶ 711. Dr. Mitchell’s analysis fails to address the impacts of changing the specific conjugated lipid or lipid concentration, which I discuss below at Section X.D.4.d.ii.

(B) Way (<2mol% Conjugated Lipid / PEG Range Limitations).

596. Dr. Mitchell’s finding that “the PEG lipid and its mol % concentration in drug product lots of the Accused Product, including within lots formulated with the PVU, v1, and v2 Formulations, [] perform[s] substantially the same function of the conjugated lipid of the Asserted Claims, including its recited mol %, in substantially the same way” is conclusory. Mitchell Rep. ¶ 715. Dr. Mitchell articulates only that “[t]he way in which the SM-102 lipids of the drug product achieve their function is through their structure, chemical composition, and concentration” and that “the PEG lipids in all lots of Moderna’s COVID-19 vaccine drug product, regardless of the target or measured mol % of PEG in that lot, embody essentially the same structure and possess the same structural features.” Mitchell Rep. ¶¶ 715-716. Again, to the extent Dr. Mitchell relies on Moderna’s representations to the FDA, the FDA’s concepts of equivalents, comparability, and bioequivalence are different than the theory of patent infringement by the doctrine of equivalents. *See* Godshalk Rep. §§ V, VI.

(C) Result (Conjugated Lipid / PEG Range Limitations).

597. Dr. Mitchell’s finding that “the PEG lipid and its mol % concentration in drug product lots of the Accused Product, including within lots formulated with the PVU, v1, and v2 Formulations, achieve substantially the same result as the conjugated lipid mixture and its mol % in the claimed invention” likewise relies on the overbroad premise that “the result of the PEG lipid limitation, including its recited mol % in the claims, in the context of the invention as a whole, is

the effective and efficient intracellular delivery of nucleic acid." Mitchell Rep. ¶ 717. This would apply broadly to LNPs encapsulating nucleic acid. And to the extent Dr. Mitchell relies on Moderna's statements to the FDA, the FDA's concepts of equivalents, comparability, and bioequivalence are different than the theory of patent infringement by the doctrine of equivalents. *See* Godshalk Rep. §§ V, VI.

598. The evidence also shows that the concentration of PEG lipid in the formulation impacts, for example, the stability of the LNPs:

[redacted]

(D) Substantial Differences (<2mol% Conjugated Lipid / PEG Range Limitations).

599. I disagree with Dr. Mitchell's opinion that "the conjugated lipid content of each lot of Moderna's COVID-19 drug product, including lots formulated with the PVU, v1, and v2 Formulations, are insubstantially different both from one another and insubstantially different from the claimed conjugated lipid mol % limitation." Mitchell Rep. ¶ 728. To the extent Dr. Mitchell relies on Moderna's statements to the FDA or in the context of seeking FDA approval, the FDA's concepts of equivalents, comparability, and bioequivalence are different than the theory of patent infringement by the doctrine of equivalents. *See* Godshalk Rep. §§ V, VI.

(E) Hypothetical Claims (Conjugated Lipid / PEG Range Limitations).

600. I understand that the doctrine of equivalents analysis may be conducted by constructing a "hypothetical claim" and assessing whether the Accused Product would literally infringe that claim. Dr. Mitchell analyzes patent infringement based on a hypothetical claim that recites "an upper limit of 3 mol % (rather than 2 mol %) conjugated lipid." Mitchell Rep. ¶ 737. For the reasons explained below, I disagree with Dr. Mitchell's predicate statement that [redacted] and with his findings based on that false premise. Mitchell Rep. ¶¶ 737-739.

601. Additionally, for the reasons explained in Sections X.D.1 and X.D.3.a, under Plaintiffs' view of the claims and Plaintiffs' new infringement theory that focuses on the lipid content of individual lipid particles, the Certificates of Analysis do not provide evidence of the lipid content of any individual particle, and do not show that any individual particles meet Plaintiffs' and Dr. Mitchell's hypothetical claims.

ii. My Function-Way-Result Analysis

602. In my opinion, the Accused Products do not infringe the conjugated lipid range limitations of the Molar Ratio Patents pursuant to the doctrine of equivalents for at least the reasons explained in this Section.

(A) Function (<2mol% Conjugated Lipid / PEG Range Limitations).

603. In summary, when present at low levels (i.e. <2mol%) the conjugated lipids / PEG claimed in the Molar Ratio Patents promote stability of the LNP in serum for intravenous delivery without affecting immunogenicity. Meanwhile, the higher levels of 2.5 mol % PEG-DMG-2000 in the v2 Formulation [redacted]. Additionally, although I refer below to Moderna's target v2 Formulation with 2.5 mol % PEG-DMG-2000, Dr. Mitchell also contends that the claim extends to 3 mol % conjugated-lipid under the doctrine of equivalents, which I considered as part of my analysis.

(1) The Function of the <2mol% Conjugated Lipid / PEG Range Limitations in the Asserted Claims

604. The Molar Ratio Patents explain that the function of the conjugated lipid is, in part, to "prevent[] aggregation of the particle." The specification of the Molar Ratio Patents also discloses that "the SNALP of the invention are ***stable in circulation***, e.g., resistant to degradation by nucleases in serum, and are substantially non-toxic to mammals such as humans." '069 Patent at 5:58-61 (emphasis added)). And the specification of the Molar Ratio Patents explains the importance of stability for the alleged invention which related to intravenous delivery:

> A gene delivery system containing an encapsulated nucleic acid for systemic delivery should be small (i.e., less than about 100nm diameter) and should remain intact in the circulation for an extended period of time in order to achieve delivery to affected tissues. ***This requires a highly stable, serum-resistant nucleic acid-containing particle that does not interact with cells and other components of the vascular compartment. The particle should also readily interact with target cells at a disease site in order to facilitate intracellular delivery of a desired nucleic acid.***

'069 Patent at 2:27-36 (emphasis added).

605. Moreover, the specification of the Molar Ratio Patents explains:

> In certain embodiments, the present invention provides improved compositions for the delivery of interfering RNA such as siRNA molecules. In particular, the Examples herein illustrate that the improved lipid particle formulations of the invention are highly effective in downregulating the mRNA and/or protein levels of target genes. Furthermore, the Examples herein illustrate that ***the presence of certain molar ratios of lipid components results in improved or enhanced activity*** of these lipid particle formulations of the present invention. For instance, the "1:57 SNALP" and "1:62 SNALP" formulations described herein are exemplary formulations of the present invention that are particularly advantageous because they provide ***improved efficacy and tolerability in vivo, are serum-stable, are substantially non-toxic, are capable of accessing extravascular sites, and are capable of reaching target cell populations.***

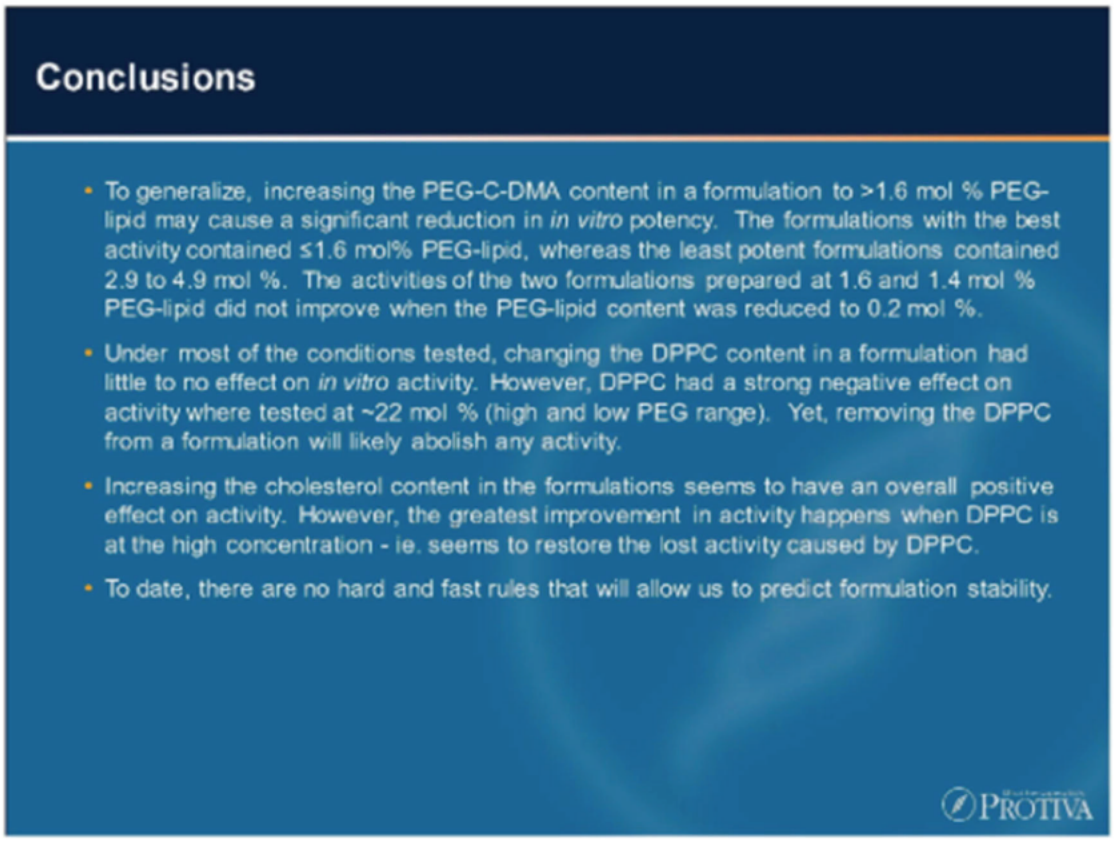
'069 Patent at 6:4-19 (emphasis added).

606. The examiner explained in the Notice of Allowance for the '069 Patent that the narrowed ranges of molar ratios was the sole basis for allowance: "The prior art of record is considered pertinent to applicant's disclosure. US 6,815,432, cited on an IDS discloses lipid formulations but does not appear to disclose the ranges for each of the lipids recited in the instant claims." *See* '069 Notice of Allowance at 6. Moreover, Arbutus relied on purported unexpected results related to low levels of conjugated lipids during the IPR: "The '435 patent is directed to the surprising discovery that nucleic acid-lipid particles with high levels of cationic lipids and ***low levels of conjugated lipids*** exhibit favorable *in vivo* transfection efficiencies, as well as 'improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described.'" '435 Appeal, D.I. 67 at 19 (emphasis added). Arbutus further explained that this "surprising discovery" solved a long-felt need material to patentability: "The nucleic acid-lipid particle formulations of the '435 patent solved a long-felt need for compositions that could safely and effectively deliver nucleic acids to target cells of patients. Skilled artisans were skeptical that compositions having high levels

of cationic lipid (i.e., 50 mol % to 85 mol %) and ***low levels of conjugated lipid*** (i.e., 0.5 mol % to 2 mol %) would be effective, let alone well-tolerated when administered *in vivo*. The combination of effectiveness and low toxicity that characterizes the claimed compositions surprised many in the field, and finally solved the delivery problem that hindered the field for decades." '435 IPR, PO Response at 2 (emphasis added).

607. From the specification and the prosecution history, a POSA would understand the function of the lower levels of PEG was to provide serum stability for IV delivery to distal sites, such as tumors or the liver, without affecting immunogenicity.

608. The importance of the low levels of PEG is reflected in a Protiva presentation titled "Formulation Development, Low-DLinDMA SNALP," which describes that Protiva found that "increasing the PEG-C-DMA content in a formulation to >1.6 mol % PEG-lipid may cause a significant reduction in *in vitro* potency."



GENV-00082361 at GENV-00082374.

(2) The Function of the 2.5 mol% PEG-DMG-2000 in the COVID-19 Vaccine:

609. [redacted] *See* Section VIII.A.4, VIII.A.3; *see also* Parsons Dep. Tr. at 212:14–214:2 [redacted], 434:2–435:18. This is dramatically different from the siRNA lipid compositions of the claimed invention, which need serum stability to reach

distal sites in the body to deliver siRNA to the target tissue, such as tumor or liver. *See* '069 Patent at 2:65-3:2; *see also* '069 Patent at 5:44-61.

(B) Way (<2mol% Conjugated Lipid / PEG Range Limitations).

610. In my opinion, the <2 mol % conjugated lipids disclosed in the Molar Ratio Patents function in a different way as compared to the 2.5 mol % SM-102 in the v2 Formulation. At a high level, the <2mol% conjugated lipids / PEG claimed in the Molar Ratio Patents functions by being present at lower levels and added in a single step with the other lipids upon forming the lipid particle. Meanwhile, the 2.5 mol % PEG-DMG-2000 in the v2 Formulation functions [redacted].

(1) The Way of the <2mol% Conjugated Lipid / PEG Range Limitations in the Asserted Claims:

611. The specification of the Molar Ratio Patents discloses a method for preparation of lipid particles in which all lipids are added in a single step before they are mixed with the siRNA, not in two or more distinct steps, and not after the LNP has formed. '069 Patent at Section VI. For example, the specification of the Molar Ratio Patents discloses a continuous mixing method:

> In certain embodiments, the present invention provides for SNALP produced via a ***continuous mixing method***, e.g., a process that includes providing an aqueous Solution comprising a nucleic acid such as an interfering RNA in a first reservoir, providing an organic lipid solution in a second reservoir, and mixing the aqueous solution with the organic lipid solution such that the organic lipid solution mixes with the aqueous solution so as to substantially instantaneously produce a liposome encapsulating the nucleic acid (e.g., interfering RNA).

'069 patent at 58:9-21 (emphasis added). The specification further explains how the method functions to produce the claimed LNP:

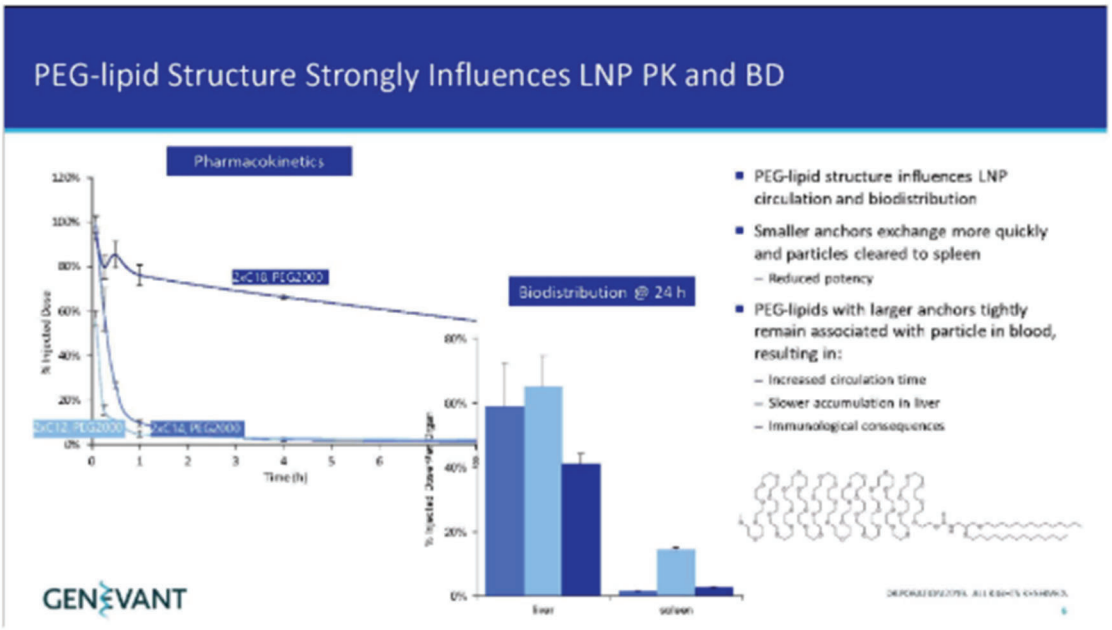
> The action of continuously introducing lipid and buffer solutions into a mixing environment, such as in a mixing chamber, causes a continuous dilution of the lipid solution with the buffer solution, thereby producing a liposome substantially instantaneously upon mixing. As used herein, the phrase "continuously diluting a

> lipid solution with a buffer solution" (and variations) generally means that the lipid solution is diluted sufficiently rapidly in a hydration process with sufficient force to effectuate vesicle generation. By mixing the aqueous solution comprising a nucleic acid with the organic lipid solution, the organic lipid solution undergoes a continuous stepwise dilution in the presence of the buffer solution (i.e., aqueous solution) to produce a nucleic acid-lipid particle.

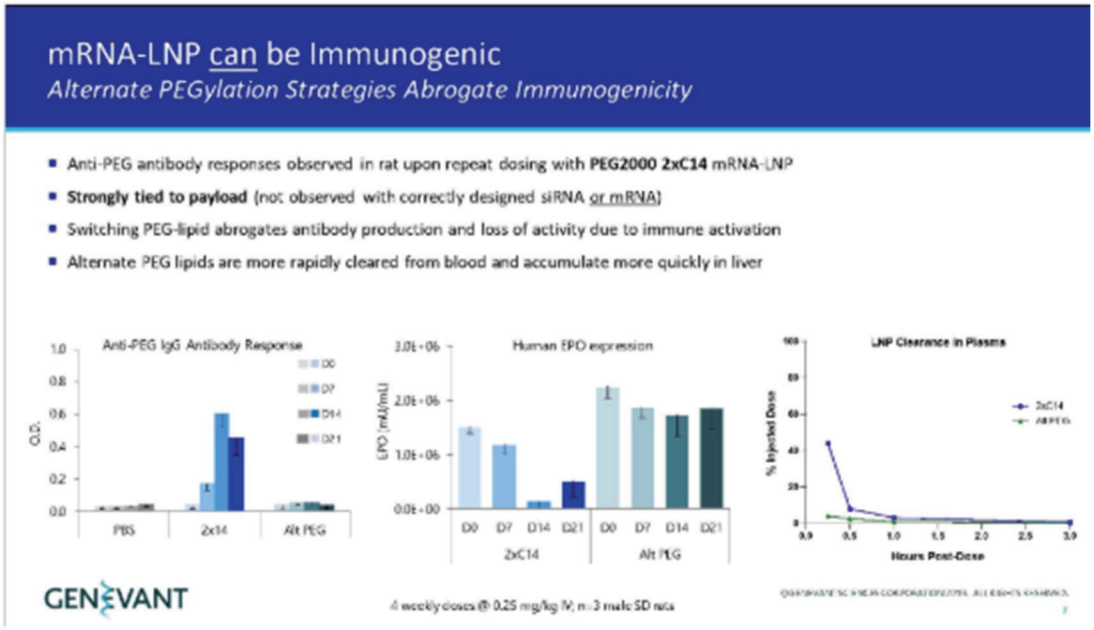
'069 patent at 58:22-35. And the specification links this process to specific attributes of the lipid particles, which "thus formed do not aggregate and are optionally sized to achieve a uniform particle size." '069 patent at 58:22-35. The specification of the Molar Ratio Patents also discloses "direct dilution processes." '069 patent at 58:43-59:16. The specification of the Molar Ratio Patents also links this process to specific attributes of the nucleic acid-lipid particles, which "thus formed do not aggregate and are optionally sized to achieve a uniform particle size." '069 patent at 59:121-22. Each of these methods describe adding the lipids in a single step, with no post addition of the PEG-lipid.

612. Dr. Mitchell claims that the Molar Ratio Patents describe post-insertion techniques (¶ 143), however, as explained above, that is a mischaracterization of the disclosures of CPL lipids [redacted]. *See* ¶¶ 131–137.

613. A Genevant presentation titled "Strategies for the Delivery of Nucleic Acid Therapeutics" dated November 14, 2019 explains how "PEG-lipid Structure Strongly Influences LNP PK and BD":



GENV-00285086 at GENV-00285091. And the Genevant presentation explains that there is an interplay between PEG and immunogenicity, and that the immunogenicity is strongly tied to payload:



GENV-00285086 at GENV-00285092.

(2) The Way of the 2.5 mol% PEG-DMG-2000 in the COVID-19 Vaccine

614. As explained above, Moderna recognized an interest in "[redacted]" MRNA-GEN-00539393 at 400-401; *see also* Parsons Dep. Tr. at 431:9-432:12 ([redacted]); Smith Dep. Tr. at 156:19-159:7 (same).

615. Moderna's formulation development for its COVID-19 vaccine supports my opinions. For example, [redacted]. Smith Dep. Tr. at 154:17–157:18, 161:4–16. [redacted]. Smith Dep. Tr. at 150:4–163:22, 17:18–19:18, 168:17-172:5. This is also reflected in deposition testimony of Moderna's fact witnesses including Don Parsons, Jack Kramarczyk, Orn Almarsson, Stephen Hoge, Mike Smith. *See, e.g.,* Parsons Dep. Tr. at 118:1-19 ("Q: Okay. What was the overview of a timeline of the changes that Moderna made to its lipid molar ratio formulation in its COVID-19 vaccine? A: We made two changes. One was to adopt the mol ratio for SM-102 and cholesterol and DSPC that we had developed as part of our platform. We did that associated with the initial scaleup of the manufacturing process from the PVU scale to what we called scale A. And then the second change was made subsequently to incorporate the higher level of PEG that we had also developed as part of our overall SM-102 LNP platform, and we did that as we were expanding the range of drug product compositions [redacted],

428:3-13 ([redacted]); Kramarczyk Dep. Tr. at 33:17-34:6 [redacted] 47:16-48:12 [redacted] ; Almarsson Dep. Tr. at 103:13-21 [redacted]); Hoge Dep. Tr. at 35:16-19 ("Q: [redacted] 251:10-253:9

[redacted]

[redacted] Smith Dep. Tr. at 207:19-208:7 [redacted]

616. [redacted]. *See* Section VIII.A.3.b. The "way" in which 2.5mol% PEG [redacted] in Moderna's COVID-19 Vaccine has a significant impact on the result. [redacted] MRNA-GEN-00508546 at 56–57. [redacted] *Id.* at 58–59; *see also* MRNA-GEN-00487212.

617. [redacted]

618. [redacted]

[redacted]

Parsons Dep. Tr. at 212:14-214:1; *see also* Parsons Dep. Tr. at 17:16-19:7.

619. [redacted]

Parsons Dep. Tr. at 434:9-435:18.

620. Further, Plaintiffs' documents show that they monitored what Moderna was doing with PEG addition and reflect improvements associated with this new process. *See, e.g.,* GENV-00403231 (Genevant internal e-mail chain with the subject line "Moderna – PEG post-insertion" noting positive effect on potency).

621. Further confirming that the "way" is different, Plaintiffs' documents confirm that using higher levels of PEG than claimed led to unfavorable results, whereas those same negative attributes are not applicable to the 2.5 mol % used in Moderna's COVID-19 Vaccine. *See, e.g.* MRNA-GEN-00508546 at 56–59. For example, the inventors found that higher levels of PEG has negative impact on in vitro efficacy, and stability. GENV-00126198-348 at GENV-00126202

("Modest increases in PEG-c-DMA concentration have a strong negative effect on in vitro efficacy"), at 208 (increasing PEG-C-DMA content in the formulation has a negative effect on in vitro activity. High PEG surfactant concentration results in smaller particles and possibly a reduction in encapsulation efficiency. The smaller particles appear to be less stable with storage."), at 214 ("when DLinDMA (-) and DPPC (+) - increasing PEG had a negative effect"); GENV-00063772, 73 at 78 (similar findings); GENV-00058026 at 032 (table Dr. Mitchell identified as underlying the Molar Ratio Patents, Table 2, shows higher PEG formulations at 2/3/4 mol% performed the worst, e.g. Sample 13 with 2.8mol% PEG had a 10x higher IC-50 than Sample 9, the 1:57 formulation); GENV-00109171 at 72 ("1:57 … slightly more potent than the 2:40 formulation …. Likely due to the 1:57 particles being less shielded by PEG-lipid") at 73 (1:57 reportedly more stable than 2:40, with other higher PEG formulations showing much poorer stability) at 74 ("reducing the cationic lipid by increasing cholesterol, DPPC, and PEG-C-DMA caused loss of activity. The activity of the 2:40 formulation was increased by halving the PEG-lipid concentration"), at 78 (similar), at 79 ("Conclusion – maximize the cationic lipid content in the formulation to improve activity"). During development of Moderna's COVID-19 Vaccine, by comparison, [redacted]. *See* Section VIII.B.

(C) Result (<2mol% Conjugated Lipid / PEG Range Limitations).

622. At a high level, the <2 mol % conjugated lipids / PEG claimed in the Molar Ratio Patents provide serum stability for the LNP to remain stable during intravenous delivery to distal sites. Meanwhile, the 2.5 mol % PEG-DMG-2000 in the v2 Formulation is [redacted].

(1) The Result of the <2mol% Conjugated Lipid / PEG Range Limitations in the Asserted Claims

623. The specification of the Molar Ratio Patents explains that there are distinct benefits of a lipid particle comprising 0.5 mol % to about 2 mol % of a lipid conjugate and that these distinct benefits were material to the patentability of the Molar Ratio Patents. Specifically, the specification explains:

> ***The present invention is based, in part, upon the surprising discovery that lipid particles comprising*** from about 50 mol % to about 85 mol % of a cationic lipid, from about 13 mol % to about 49.5 mol % of a non-cationic lipid, and ***from about 0.5 mol % to about 2 mol % of a lipid conjugate provide advantages when used for the in vitro or in vivo delivery of an active agent, such as a therapeutic nucleic acid (e.g., an interfering RNA).*** In particular, as illustrated by the Examples herein, the present invention ***provides stable nucleic acid-lipid particles (SNALP) that advantageously impart increased activity of the encapsulated nucleic acid*** (e.g., an interfering RNA such as siRNA) and ***improved tolerability of the formulations in vivo***, resulting in a ***significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described***. Additionally, the SNALP of the invention are ***stable in circulation***, e.g., ***resistant to degradation by nucleases in serum***, and are substantially non-toxic to mammal***s*** such as humans. As a non-limiting example, FIG. 3 of Example 4 shows that one SNALP embodiment of the invention ("1:57SNALP) was more than 10 times as efficacious as compared to a nucleic acid-lipid particle previously described ("2:30 SNALP) in mediating target gene silencing at a 10-fold lower dose. Similarly, FIG. 2 of Example 3 shows that the "1:57 SNALP" formulation was substantially more effective at silencing the expression of a target gene as compared to nucleic acid-lipid particles previously described ("2:40 SNALP).
>
> In certain embodiments, the present invention provides improved compositions for the delivery of interfering RNA such as siRNA molecules. In particular, the Examples herein illustrate that the improved lipid particle formulations of the invention are highly effective in downregulating the mRNA and/or protein levels of target genes. Furthermore, the Examples herein illustrate that ***the presence of certain molar ratios of lipid components results in improved or enhanced activity of these lipid particle formulations of the present invention***. For instance, the "1:57 SNALP and "1:62 SNALP formulations described herein are exemplary formulations of the present invention that are particularly advantageous because they provide improved efficacy and tolerability in vivo, ***are serum-stable, are substantially non-toxic, are capable of accessing extravascular sites, and are capable of reaching target cell populations.***

'069 Patent at 5:44-6:19 (emphasis added). This is consistent with inventor testimony that the inventors had to reduce PEG content below 2 mol% to improve stability, which is the opposite result to Moderna's findings that increasing PEG above 2 mol% improved stability, as described below. Yaworski Dep. Tr. 63:14–20 (Referring to colloidal instability with the 2:40 formulation, with 2 mol% PEG) and 78–80 ("One of the surprising discoveries from this 1:57 work that we had done is that we went the opposite. We ***reduced*** the concentration of PEG lipid in the formulation, against all principles that we understood, yet this 1:57 formulation showed ***better*** colloidal stability.") (emphasis added). Additionally, the inventor Mr. Yaworksi noted that PEGs role was to ensure stability for systemic delivery to distal target cites, which is not applicable to Moderna's use of PEG in its COVID-19 Vaccine. Yaworski Dep. At 19 ("… the PEG lipid has a very important role in vivo. So when we inject these particles into the circulation, quite often they're, you know, interacting or being bound, or what we say is austenized [sic]. There's a lot of proteins, there's a lot of cellular interactions. These PEG lipids provide the particle with some shielding to prevent rapid elimination or clearance to the reticuloendothelial system, which is a concern if you're trying to deliver drug to cells."). The same testimony confirms Moderna's use of 2.5mol% PEG must operate in a different "way" because it achieved diametrically opposite results.

624. As explained in Section X.D.4.d.ii(A)(1), the prosecution history of the patents-in-suit further supports the distinct benefits of a lipid particle comprising 0.5 mol % to about 2 mol % of a lipid conjugate. Indeed, the examiner explained in the Notice of Allowance that the narrowed ranges of molar ratios was the sole basis for allowance: "The prior art of record is considered pertinent to applicant's disclosure. US 6,815,432, cited on an IDS discloses lipid formulations but does not appear to disclose the ranges for each of the lipids recited in the instant claims." *See* '069 Notice of Allowance) at 6.

625. Moreover, Arbutus repeated this disclaimer and reliance on unexpected results during IPR: "The '435 patent is directed to the surprising discovery that nucleic acid-lipid particles with high levels of cationic lipids and ***low levels of conjugated lipids*** exhibit favorable *in vivo* transfection efficiencies, as well as 'improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described.'" '435 Appeal, D.I. 67 at 19 (emphasis added). Arbutus further explained that this "surprising discovery" solved a long-felt need material to patentability: "The nucleic acid-lipid particle formulations of the '435 patent solved a long-felt need for compositions that could safely and effectively deliver nucleic acids to target cells of patients. Skilled artisans were skeptical that compositions having high levels of cationic lipid (i.e., 50 mol % to 85 mol %) and ***low levels of conjugated lipid*** (i.e., 0.5 mol % to 2 mol %) would be effective, let alone well-tolerated when administered *in vivo*. The combination of effectiveness and low toxicity that characterizes the claimed compositions surprised many in the field, and finally solved the delivery problem that hindered the field for decades." '435 IPR, PO Response at 2 (emphasis added). Additionally, Arbutus distinguished their alleged invention of "a nucleic acid-lipid particle comprised of relatively high levels of cationic lipids and low levels of conjugated lipids" from the prior art, "The claimed invention is a nucleic acid-lipid particle comprised of relatively high levels of cationic lipids and ***low levels of conjugated lipids***." '069 IPR, PO Response at 29 (emphasis added).

(2) The Result of the 2.5 mol% PEG-DMG-2000 in the COVID-19 Vaccine

626. Increased PEG (2.5 mol % in v2 Formulation vs. 1.5 mol% in v1 Formulation) [redacted]. *See* Parsons Dep. Tr. at 238:5-239:4 [redacted]

[redacted]

(emphasis added). At his deposition, Dr. Parsons explained that [redacted]

Parsons Dep. Tr. 431:1-432:21. *See also* MRNA-GEN-00635648 at 750 [redacted]

627. [redacted]

> Q: Okay. Moderna ultimately switched to a formulation with 48 percent SM-102 correct? We've talked about that a bit.
>
> A: Yes, we have. Yes.
>
> Q: [redacted]

[redacted]

See Parsons Dep. Tr. at 147:4-148:6 (emphasis added). [redacted]. *See* MRNA-GEN-01266205 at -266 [redacted] MRNA-GEN-01691921 (similar); MRNA-GEN-01692106; *see also* Parsons Dep. Tr. at 438:9-440:16 [redacted]

[redacted] This is in sharp contrast to the Molar Ratio Patents, which have the goal of extended serum stability for the siRNA lipid particles to reach distal target sites (i.e. the lipid particles are designed to ***not*** break down rapidly once administered). *See, e.g.,* '069 Patent at 2:27-36 ("A gene delivery system containing an encapsulated nucleic acid for systemic delivery should be small (i.e., less than about 100 nm diameter) and should remain intact in the circulation for an extended period of time in order to achieve delivery to affected tissues. This requires a highly stable, serum-resistant nucleic acid-containing particle that does not interact with cells and other components of the vascular compartment. The particle should also readily interact with target cells at a disease site in order to facilitate intracellular delivery of a desired nucleic acid."). [redacted] *See, e.g.* MRNA-GEN-00508546 at 56–59; s*ee also* Section VIII.B, and VIII.A.

(D) Substantial Differences (Conjugated Lipid / PEG Range Limitations).

628. In my opinion, the physical and chemical properties of 2.5 mol % PEG-DMG-2000 in Moderna's SPIKEVAX® v2 Formulation are substantially different from the physical and

[49] Dr. Mitchell argues that "contemporaneous documentation [] does not support [this] assertion" because the document "does not indicate that this issue with the failed internal specification arose due to the 50:10:38.5:1.5 formulation." Mitchell Rep. at ¶ 266. But Dr. Mitchell provides no other explanation for the failed specification. Instead, Dr. Mitchell relies on the fact that Moderna continued to use the 50:10:38.5:1.5 formulation in other contexts, including the PVU formulation. Mitchell Rep. at ¶ 266-267.

chemical properties of the claimed lipid ranges in the Molar Ratio Patents. This is consistent with the conclusions of my above analysis in terms of function, way, and result. The substantial differences may be explained by the specific mol % concentration of PEG-DMG-2000 in Moderna's SPIKEVAX® v2 Formulation. For example, as explained above, increased PEG (2.5 mol % in v2 Formulation vs. 1.5 mol% in v1 Formulation), [redacted] *See* Parsons Dep. Tr. at 238:5-239:4 [redacted] (emphasis added).

629. Additionally, Dr. Mitchell does not acknowledge that in his opinion, the v2 formulation infringes under the doctrine of equivalents despite not meeting up to three distinct claim elements literally: limitations of the '435 Patent claims requiring less than 49.5 mol% non-cationic lipid, the limitations of all Molar Ratio Patents requiring 2 mol% or less PEG/conjugated lipid and the limitations of '435, '069, '668 and '359 claims requiring more than 50 mol% cationic lipid. The fact that Moderna's v2 formulation does not literally meet up to three independent and distinct limitations further supports my opinion that the differences are far more than substantial.

630. In sum, the evidence that I discuss in the function/way/result framework shows that the 2.5 mol % PEG-DMG-2000 in Moderna's SPIKEVAX® v2 Formulation is substantially different from claimed <2 mol % conjugated lipid ranges in the Molar Ratio Patents.

iii. Prosecution History Estoppel (Conjugated Lipid / PEG Range Limitations)

631. In my opinion, prosecution history estoppel precludes Plaintiffs' arguments that Moderna's v2 Formulation infringes all Asserted Claims requiring "from 0.5 mol % to 2 mol %" or "from 0.1 mol % to 2 mol %" of a conjugated lipid that inhibits aggregation (including dependent claims reciting narrower ranges) under the doctrine of equivalents based on narrowing claim amendments and based on arguments during prosecution that would lead a competitor to rely on disclaimers of claim scope by the applicant during prosecution of the '069 patent. In my opinion, prosecution history estoppel would also preclude Plaintiffs from arguing Moderna's v2 Formulation infringes any Asserted Claims of the '359, '668,'435, and '378 patents requiring "from 0.5 mol % to 2 mol %" or "from 0.1 mol % to 2 mol %" of a conjugated lipid (including dependent claims reciting narrower ranges) under the doctrine of equivalents because the '359, '668,'435, and '378 patents issued from continuation applications of the '069 patent and use the same claim terms as in the '069 patent, and because narrowing amendments were made during prosecution.

632. In my opinion, the applicant amended their patent claims to be narrower and did so for the purpose of patentability. During prosecution of the '069 patent, the examiner rejected the claims as being anticipated by MacLachlan, et al. (US 2006/0008910), which "teaches the SNALP wherein the cationic lipid is from about 2 mol % to about 60 mol % of the total lipid present in the particle (paragraph 85), the phospholipid is from about 5% to about 90% or from about 10% to about 85% of the total lipid present in the particle (paragraph 85), the cholesterol is from about

20% to about 55% of the total lipid present in the particle (paragraph 85, top of page 8), and the conjugated lipid is from about 1 % to about 20% of the total lipid present in the particle (paragraph 85).” ’069 File History May 12, 2011 at 2-4. The examiner tied the rejection to the inclusion of “about” in the claims explaining:

> The claims are further directed to the particle wherein the nucleic acid is a siRNA, the relative amounts of components read on a broad range of amounts because of the term ‘comprising about’. The applicants do not provide a definition of the term in the specification. Thus, ‘comprising about’ could embrace an amount+/- 10, 20, 30 mol % of a lipid component.

’069 File History May 12, 2011 at 2. The examiner further provided a comparison of the lipid components in the application and MacLachlan:

Application	MacLachlan
instant claims of ‘367 1) cationic lipid comprising from about 50-65 mol % 2) phospholipid comprises from about 4-10 mol % 3) cholesterol comprising from about 30-40 mol% 4) conjugated lipid comprising from about 0.5-2 mol%	pre-grant US publication (paragraph 0085) 1) cationic lipid 2-60, 5-50, 10-45, 20-40, 30 mol% 2) phospholipid 5-90 mol% 3) cholesterol 20-55 mol % 4) conjugated lipid 1-20 mol %

’069 File History May 12, 2011 at 3-4. The examiner further rejected pending claims as obvious in view of Maclachlan, et al. (US 2006/0008910) and further in view of Fosnaugh, et al. (US 2003/0143732). ’069 File History May 12, 2011 at 5-6. The examiner explained:

> In response to applicant's argument that Fosnaugh and Maclachlan do not teach or suggest 1:57 SNALP formulation and their new and unexpected results, the argument is not found persuasive because while it is acknowledged that 1 :57 shows a new an unexpected result, the product recited in the instant claims read on broad range of SNALP formulations, including 2:30 and 2:40 because of the term ‘comprising from about’. The term is broad because the specification does not provide a definition of the term and the term could read on SNALP formulations other than 1 :57, e.g., 2:30 and 2:40.

'069 File History May 12, 2011 at 6. The examiner further rejected pending claims as invalid for obviousness-type double patenting over reference claims that recited overlapping ranges. '069 File History May 12, 2011 at 7-14. After examiner interviews, the applicant amended the claims to remove "about":

1. (Currently amended) A nucleic acid-lipid particle comprising:

(a) a nucleic acid;

(b) a cationic lipid comprising from ~~about~~ 50 mol % to ~~about~~ 65 mol % of the total lipid present in the particle;

(c) a non-cationic lipid comprising a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the phospholipid comprises from ~~about~~ 4 mol % to ~~about~~ 10 mol % of the total lipid present in the particle and the cholesterol or derivative thereof comprises from ~~about~~ 30 mol % to ~~about~~ 40 mol % of the total lipid present in the particle; and

(d) a conjugated lipid that inhibits aggregation of particles comprising from ~~about~~ 0.5 mol % to ~~about~~ 2 mol % of the total lipid present in the particle.

'069 File History Aug. 11, 2011 at 2. The applicant explained:

> During the interview, Applicants' representatives proposed amending the claims to delete the word 'about' from the ranges of lipid components and argued that the claimed ranges were not anticipated by MacLachlan *et al.* (US2006/0008910) because that reference failed to disclose the claimed ranges with sufficient specificity as required by M.P.E.P 2131.03 (II) and *Atofina*.

'069 File History Aug. 11, 2011 at 6. The applicant argued:

> In making both rejections, the Examiner alleges that the term 'comprising from about' recited in the instant claims embraces a broad range of lipid components. In an earnest effort to expedite prosecution, but without acquiescing on the merits of the rejection, Applicants have amended the claims to delete 'about' from the ranges of lipid components recited therein.

'069 File History Aug. 11, 2011 at 7. The applicant further provided a comparison of the ranges of lipid components in the amended claims and MacLachlan:

Lipid Component	Claim 1 as Amended	US 2006/0008910*
Cationic Lipid	50-65 mol %	"2-60, 5-50, 10-45, 20-40, 30 mol%"
Phospholipid	4-10 mol %	"5-90 mol%"
Cholesterol	30-40 mol %	"20-55 mol %"
Conjugated Lipid	0.5-2 mol %	"1-20 mol %"

*The ranges set forth in this column are reproduced from page 4 of the Office Action mailed May 12, 2011.

'069 File History Aug. 11, 2011 at 8. As also explained above at Sections X.D.3.b.iii and X.D.4.c.iv, when the applicant disclaimed "about" (which examiner defined as 10/20/30%), they disclaimed variation that "about" previously encompassed (*e.g.*, +/- 0.01% to +/-30) from each of the claimed ranges. For the conjugated lipid, the applicant therefore disclaimed from 2 mol % to 32 mol % when removing the word "about."

633. Ultimately, the examiner explained in the Notice of Allowance for the '069 patent that the narrowed ranges of molar ratios was the sole basis for allowance: "The prior art of record is considered pertinent to applicant's disclosure. US 6,815,432, cited on an IDS discloses lipid formulations but does not appear to disclose the ranges for each of the lipids recited in the instant claims." *See* '069 Notice of Allowance at 6. A POSA would understand from this that the arguments and amendment deleting the word "about" were made to overcome rejections from the Examiner, including prior-art rejections, and that the arguments and amendments were successful in getting the claims allowed by the Examiner (in other words, those amendments and arguments were clearly made for purposes of patentability).

634. Similarly, Plaintiffs amended their patent claims of the '359, '668,'435, and '378 patents to be narrower and did so for the purpose of patentability. Plaintiffs are estopped from asserting doctrine of equivalents to capture more than 2 mol % of a conjugated lipid or PEG-lipid conjugate for the '359, '668, '435, and '378 patents. During prosecution of the '359, '668, and '435 patents, for example, the applicants filed preliminary amendments to delete "about" from

original claims reciting "a conjugated lipid . . . comprising from *about* 0.5 mol % to *about* 2 mol % of the total lipid." *See*, *e.g.*, '359 File History October 5, 2011 at 114, March 28, 2012 at 4; '668 File History June 26, 2013 at 114, Nov. 6, 2013 at 5; '435 File History August 18, 2014 at 114, Feb. 26, 2015 at 2 (emphasis added). Similarly, when pursuing the '378 patent, the applicants filed claims reciting a nucleic acid-lipid particle consisting essentially of a PEG-lipid conjugate ***consisting*** of "from 0.1 mol % to 2 mol % of the total lipid present in the particle," after narrowing its claims when prosecuting the '069, '359, '668, and '435 patents. *See, e.g.*, '378 File History Apr. 12, 2021 at 121. Without these amendments, applicant would have known from the earlier '069 prosecution that the claims would face rejection again over the prior art, confirming the amendments were made for patentability. Moreover, the disclosure in the specification demonstrates that applicants knew how to claim fractional percentages of the conjugated lipid. '359 patent at 22:40–52 (listing ranges for the conjugated lipid including fractional percentages such as from about 1.2 mol % to about 1.7 mol %, from about 1.3 mol % to about 1.6 mol %, or about 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mol % (or any fraction thereof or range therein) of the total lipid present in the particle); 57:24–35.

635. Because the '359, '668, '435, and '378 patents are issued from continuation applications of the '069 patent and use the same PEG/conjugate claim terms as those in the '069 patent (reciting conjugated lipid amounts in mol % ranges), Plaintiffs are estopped from arguing that Moderna's v2 Formulation infringes any Asserted Claims of the '359, '668, '435, and '378 patents requiring from 0.1 or 0.5 mol % to 2 mol % of a conjugated lipid under doctrine of equivalents. At no point during prosecution of the later '359, '668, and '435 patents did the applicant inform the Examiner that the disclaimer was withdrawn, and that the pending claims in

those later patent applications needed to be examined again in light of the prior art such as MacLachlan.

636. I understand that when surrendering claim scope for reasons related to patentability, as the applicant did here, there is a presumption that applicant has surrendered everything between the original claim limitation and the amended claim limitation. The applicant never responded to the examiner to state that it intended to disclaim any amount less than +/-30% variability. Therefore, when the applicant disclaimed "about" (which examiner defined as +/-10/20/30%), it disclaimed every variation leading up to that (*e.g.*, +/- 0.00001% to +/-30). I further understand that the Court has already found that by removing the word "about," the applicant disclaimed variability of "+/- 10, 20, 30 mol %" from the claims. D.I. 266 (Memorandum Opinion re Claim Construction) at 21 ("a claimed range of 'about' 50–65 mol % could potentially encompass a range as small as 40–75 mol % and as large as 20–95 mol %.[7] When Plaintiff removed the phrase 'comprising about,' it only ***clearly disclaimed these broader ranges*** and not the scientific conventions of rounding") (emphasis added). Although the quote from the Court above discussed "about" in the context of cationic lipid, in my opinion the removal of "about" from the conjugated lipid component would have similar results, where the amount of variability for conjugated lipid could potentially encompass up to 32 mol % conjugated lipid as noted in the table below.

637. Based on the Examiner's definition of "about", which the applicant accepted, the claims before and after the amendment are as follows:[50]

[50] As noted above at ¶ 312, throughout this section I do not explicitly refer to rounding for simplicity, but I do apply the Court's claim construction.

	Original claim 1 as of 1/31/2011	Amended claim	Scope of surrendered territory	v2 Formulation
Cationic Lipid	About 50 mol % to about 65 mol % (20 to 95 mol %)	50 mol % to 65 mol %	<50 mol % and 65 to 95 mol %	48.0 mol %
Phospholipid	About 4 mol % to about 10 mol % (0.0 to 40 mol %)	4 mol % to 10 mol %	<4 mol % and 10 to 40 mol %	11.0 mol %
Cholesterol	About 30 mol % to about 40 mol % (0.0 to 70 mol %)	30 mol % to 40 mol %	<30 mol % and 40 to 70 mol %	38.5 mol %
Conjugated lipid	About 0.5 to about 2 mol% (0.0 to 32 mol %)	0.5 mol % to 2 mol %	>2 to 32 mol%	2.5 mol %

As shown above, Moderna's v2 Formulation has 2.5 mol % conjugated lipid, which falls within the scope of the surrendered territory. Although I show the '069 claims above as an example, the same analysis applies for the related '435, '668, '359, and '378 patents (as to the conjugated lipid component).

638. In my opinion, a nucleic acid-lipid particle comprising 2.5 mol % conjugated lipid that inhibits agreement (or any amount between 2 mol % and 3 mol %) was foreseeable to a POSA at the time the applicant made their narrowing amendment. As demonstrated in the file history, the prior art disclosed incremental percentages of lipid components in nucleic acid-lipid particles. *See, e.g.*, '069 File History May 12, 2011 at 3-4 (examiner summarizing disclosures of MacLachlan, U.S. 2006/0008910); '069 File History Aug. 11, 2011 at 8 (same). During prosecution, the examiner also explained:

> In response to applicant's argument that Fosnaugh and Maclachlan do not teach or suggest 1:57 SNALP formulation and their new and unexpected results, the argument is not found persuasive because while it is acknowledged that 1 :57 shows

> a new an unexpected result, the product recited in ***the instant claims read on broad range of SNALP formulations***, including 2:30 and 2:40 ***because of the term 'comprising from about'***. The term is broad because the specification does not provide a definition of the term and the term could read on SNALP formulations other than 1:57, e.g., 2:30 and 2:40.

'069 File History May 12, 2011 at 6 (emphasis added). This explanation further supports estoppel because it shows that the equivalents were foreseeable. In other words, the applicant already had an earlier patent to the 2:40 formulation with overlapping ranges, as raised by the examiner, showing that the applicant knew that other ranges and amounts of lipids existed and chose to disclaim greater than 2 mol % conjugated lipid. Likewise, the specification of the '069 Patent was drafted with incremental percentages, showing the ability to describe incremental variation in lipid mol %. *See, e.g.*, '069 Patent at 22:30–42, 57:12–23; Table 2 formulations (*e.g.*, Samples 7, 8, 13–15).

639. Additionally, based on my review of the file histories, the applicant's reasons for the claim amendments were not tangential to the alleged equivalent (i.e., nucleic acid-lipid particles comprising >2 mol % conjugated lipid). As I described above, these claim amendments to remove "about" were made to overcome rejections of the prior art that taught overlapping ranges of mol % conjugated lipid, and specifically an embodiment comprising about 2 mol % conjugated lipid referred to as the "2:40" formulation. Nor do I see another reason that would have prevented Plaintiffs from describing and claiming nucleic acid-lipid particles comprising lower mole percentages of cationic lipid. As I described above, nucleic acid-lipid particles comprising varying amounts and ranges of cationic lipid were routinely described in the prior art and Plaintiffs were capable of doing so in the specification.

640. Reviewing the arguments Plaintiffs made when amending the claims described above, as well as emphasizing the narrowness of the claims compared to the prior art overlapping

ranges, a competitor would reasonably believe that Plaintiffs were effectively surrendering and disclaiming nucleic acid-lipid particles comprising greater than 2 mol % conjugated lipid.

641. Further supporting the argument-based estoppel, Plaintiffs also repeatedly argued in *inter partes* review ("IPR") the alleged unexpected results and purported innovative aspects of the invention arising from "low levels of conjugated lipids (0.5–2 mol %)" in an attempt to distinguish prior art. For example, during the IPR for the '069 patent, Plaintiffs alleged:

> The '069 patent is directed to the ***surprising discovery that nucleic acid-lipid particle formulations with high levels of cationic lipids and low levels of conjugated lipids*** exhibit favorable *in vivo* transfection efficiencies as well as "improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index [a measure of dosage relative to toxic effect] as compared to nucleic acid-lipid particle compositions previously described." . . . ***Reflecting this discovery, the '069 patent claims nucleic acid-lipid particle formulations with high levels of cationic lipids (50–65 mol %) and low levels of conjugated lipids (0.5–2 mol %)***—as well as specific levels of cholesterol/derivative (30-40 mol %) and phospholipid (4-10 mol %).

IPR2019-00554, Paper 7 (Patent Owner's Preliminary Response) at 13, 14, 45–46; IPR2019-00554, Paper 15 (Patent Owner's Response) at 7, 8, 29–30, 32, 62, 64.

642. During the IPR for the related '435 patent, Plaintiffs again alleged:

> The '435 patent discloses the ***"surprising discovery" that nucleic acid-lipid particle formulations with a high level of cationic lipid and a remarkably low level of conjugated lipid*** exhibited favorable in vivo transfection efficiencies as well as "improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index [a measure of dosage relative to toxic effect] as compared to nucleic acid-lipid particle compositions previously described." . . . ***Reflective of this discovery, the '435 patent claims nucleic acid-lipid particle formulations with a high level of cationic lipid (50–85 mol %) and an unconventionally low level of conjugated lipid (0.5–2 mol %).***

IPR2018-00739, Paper 12 (Patent Owner's Preliminary Response) at 2, 6–8, 12, 24, 37; id., Paper 24 (Patent Owner's Response) at 2, 14, 19–21, 32, 47, 59.

643. Plaintiffs further made statements during Appeal No. 20-1184 that made it clear that the end of the recited range of conjugated lipid was 2.0 and not higher. D.I. 67-1 at 64–65

("L054 has the starting composition including 2% conjugated lipid (PEG-n-DMG), which is ***right at the edge*** of the 0.5 mol% to 2 mol% range claimed in the '435 Patent.") (emphasis added).

644. From these arguments, a competitor would reasonably believe that Plaintiffs were effectively surrendering and disclaiming nucleic acid-lipid particles comprising greater than 2 mol % conjugated lipid, particularly because they distinguished claims of the '069 and '435 patents reciting "from 0.5 mol % to 2 mol %" of cationic lipid (including dependent claims reciting narrower ranges) from formulations in the prior art that start at 2 mol % conjugated lipid. Therefore, it is my understanding that these arguments preclude Plaintiff from now recapturing nucleic acid-lipid particles claimed with greater than 2 mol % conjugated lipid under the '069 and '435 patents, as well as the '359, '668, and '378 patents, which are in the same family as the '069 and '435 patents and similarly claim "an unconventionally low level of conjugated lipids" (0.5–2 mol % or 0.1–2 mol %).

iv. Public Dedication

645. Plaintiffs are precluded from asserting that any Asserted Claims of the '069, '359, '668, and '435 patents cover the v2 Formulation because the specification of the patents discloses the unclaimed subject matter such that it has been dedicated to the public.

646. For example, the specification of the '069 patent discloses embodiments that contain a conjugated lipid (e.g., PEG-lipid conjugate) comprising "about 2 mol %" of the total lipid:

> In certain instances, the conjugated lipid that inhibits aggregation of particles (e.g., PEG-lipid conjugate) may comprise from about 0.1 mol % to about 2 mol %, from about 0.5 mol % to about 2 mol %, from about 1 mol % to about 2 mol %, from about 0.6 mol % to about 1.9 mol %, from about 0.7 mol % to about 1.8 mol %, from about 0.8 mol % to about 1.7 mol %, from about 1 mol % to about 1.8 mol %, from about 1.2 mol % to about 1.8 mol %, from about 1.2 mol % to about 1.7 mol %, from about 1.3 mol % to about 1.6 mol %, from about 1.4 mol % to about 1.5 mol %, or about 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mol % (or any fraction thereof or range therein) of the total lipid present in the particle.

See, e.g., '069 patent at 22:30–42, 68:39–48.[51] As explained above, *see, e.g.*, ¶¶ 513, 582, 637, Plaintiffs accepted the examiner's definition of "about" being +/-10/20/30 mol%, which means "about 2 mol%" is expanded to 32 mol%. The passage from the specification confirms that when Plaintiffs wanted to expressly refer to incrementally varied percentages of PEG, they were able to. Additionally, the specification refers to various formulations with more than 2 mol% PEG. *See, e.g.* '069 Patent at Table 2 (formulations with 3.9, 2.7, 2.5, 3.6, 2.8, 2.6 mol% PEG); Table 4 (formulation with 2.2 and 2.5 mol% PEG). Because the '069, '359, '668, '435, and '378 patents claim a nucleic acid-lipid particle comprising a conjugated lipid consisting of "from 0.5 mol % to 2 mol %" or "from 0.1 mol % to 2 mol %" of the total lipid, while the specification discloses "from ***about*** 0.1 mol % to ***about*** 2 mol %" of a conjugated lipid (emphasis added) and various formulations with specific mol% of PEG around 2.5 to 3.5 mol%, Plaintiffs are estopped from enforcing any unclaimed embodiments comprising more than 2 mol % of a conjugated lipid, as that range has been dedicated to the public. As described above in the context of prosecution history estoppel, Plaintiffs' statements to the Patent Office during prosecution and during IPR proceedings criticizing higher PEG compositions as inferior and touting the benefits of less than 2 mol% PEG also confirm my opinion that lipid particles with more than 2 mol% were dedicated to the public.

v. Vitiation

647. I understand a claim term is vitiated when the proposed equivalent embraces a structure that is specifically excluded from the scope of the claims. Vitiating the numerical range

[51] The '069, '359, '668, and '435 patents are in the same family and share the same specification.

limitations requiring, for example, a conjugated lipid at specified mol % would deprive the public of the notice function of the claims and render the claims meaningless.

648. As explained above, the applicant disclaimed embodiments comprising more than 2 mol % of a conjugated lipid and the examiner explained in the Notice of Allowance for the '069 patent that the narrowed ranges of molar ratios was the sole basis for allowance:

> The prior art of record is considered pertinent to applicant's disclosure. US 6,815,432, cited on an IDS discloses lipid formulations but does not appear to disclose the ranges for each of the lipids recited in the instant claims.

'069 Notice of Allowance at 6. Vitiating the numerical limitations requiring a conjugated lipid at specified mol % ranges, as would be required under Plaintiffs' theories of infringement under the doctrine of equivalents, would deprive the public of the notice function of the claims and thereby render the claims meaningless. Thus, in my opinion, Plaintiffs are precluded from claiming that Moderna's v2 Formulation infringes any Asserted Claims of the '069, '359, '668, '435, and '378 patents under the doctrine of equivalents.

649. I note that Dr. Mitchell does not explain why prosecution history estoppel, vitiation, and/or public dedication should not apply in this instance. To the extent Dr. Mitchell does so later, I reserve the right to respond.

5. Moderna's SPIKEVAX® Formulations v1 and/or v2 Do Not Meet the Non-Cationic Lipid, Cholesterol, and/or Phospholipid Range Limitations of Certain Claims of the Molar Ratio Patents

650. I incorporate by reference my criticisms of Dr. Mitchell's approach to assessing infringement and the reasoning behind relying on Moderna's input data set out in at least § X.D.3.a herein. I reiterate that all of these measurements nonetheless report values for the aggregate formulation, despite the input measurements being the best measure of the composition of the LNPs in Moderna's COVID-19 vaccine, so given Plaintiffs' position that the relevant question for

c. '435 patent

660. Claim 1 of the '435 patent requires 13 to 49.5 mol % non-cationic lipid. Applying the principles of rounding, this range encompasses 12.5 to less than 49.55 mol%. I note that claim 1 is not asserted, as it was invalidated in a prior IPR brought by Moderna. All claims of the '435 patent depend directly or indirectly from claim 1, therefore I understand that all claims of the '435 patent contain this requirement.

661. As shown above, the non-cationic content in the v1 Formulation of Moderna's COVID-19 vaccine is 50 mol%. For this additional reason, formulation v1 of Moderna's COVID-19 vaccine does not literally infringe the claims of the '435 patent.

d. '668 patent

662. Claim 1 of the '668 patent requires that the non-cationic lipid comprise up to 49.5 mol%. Applying principles of rounding, this range encompasses up to, but not including, 49.55 mol%.

663. As shown above, the non-cationic content in the v1 Formulation of Moderna's COVID-19 vaccine is 50 mol%. For this additional reason, formulation v1 of Moderna's COVID-19 vaccine does not literally infringe the claims of the '668 patent.

664. Further, claim 10 of the '668 patent requires that the cholesterol comprise 30-35 mol%. Applying the principles of rounding, this range encompasses 29.5 to less than 35.5 mol%.

665. As shown above, formulations v1 and v2 of Moderna's COVID-19 vaccine comprise 38.5 mol% cholesterol. For this additional reason, neither formulation v1 nor v2 of Moderna's COVID-19 vaccine literally infringe claim 10 of the '668 patent.

e. No Infringement of Non-Cationic Lipid Range Limitations Under Doctrine of Equivalents

i. Dr. Mitchell's Function-Way-Result Analysis

articulates only that "[t]he way in which the mixture of cholesterol and DSPC of the drug product achieve their function is through their structure, chemical composition, and concentration, which enables the lipids to provide amphipathicity and hydrophobicity to help provide structure and stability as well as to promote fusogenicity." Mitchell Rep. ¶ 687. Dr. Mitchell does not compare any specific features between each of Moderna's PVU, v1 and v2 Formulations against the claim element in the asserted claims, which I discuss below in Section X.D.5.e.i(C). In fact, despite acknowledging that the ***concentrations*** of these components will affect the way in which they perform their respective functions, Dr. Mitchell does not consider how the ***concentration*** of the non-cationic components in Moderna's COVID-19 vaccine, which differs from that in the claimed particles, affects the way in which they perform their functions.

673. Again, as noted above, Dr. Mitchell's lot-to-lot comparisons and his reference to the "mRNA-LNPs" as a whole (or their mechanism of action) are not proper bases and do not support his DOE analysis.

(C) Result (Non-cationic Lipid Range Limitations)

674. Dr. Mitchell's finding that "the non-cationic lipid mixture (of cholesterol and DSPC) and its mol % concentration in drug product lots of the Accused Product, including within lots formulated with the PVU, v1, and v2 Formulations, achieve substantially the same result as the non-cationic lipid mixture and its mol % in the claimed invention" likewise relies on the overbroad premise that "the result of the non-cationic lipid limitation, including its recited mol % in the claims, in the context of the invention as a whole, is the effective and efficient intracellular delivery of nucleic acid." Mitchell Rep. ¶ 689. *See also* Mitchell Rep. ¶¶692, 694. Again, this would apply broadly to LNPs encapsulating nucleic acid. That is not the proper standard.

675. Dr. Mitchell further states that "Moderna's COVID-19 vaccine drug product, whether formulated with the PVU, v1, or v2 Formulations, including drug product formulations

with reported non-cationic lipid content values of 49.5 to 53 mol % noncationic lipid, achieve substantially the same result, including with respect to efficacy (immunogenicity), safety, and stability compared to formulations using up to 49.5 mol % noncationic lipid, including the PVU and v2 Formulations, which Moderna does not dispute meet the claimed non-cationic lipid mol % limitations." Mitchell Rep. ¶ 689. In addition to disagreeing with the broader premise of his comparison, which I note above, I also note that Dr. Mitchell appears to be equating efficacy with immunogenicity. This reveals a central flaw to his comparison. Whereas a POSA would want to observe immunogenicity when developing an mRNA vaccine, in fact, immunogenicity is a ***concern*** in the context of developing siRNA therapeutics or vaccines, which is the only payload described in the Molar Ratio Patents. For this additional reason, Dr. Mitchell's argument relating to the "result" portion of the analysis fails.

676. Further, to the extent Dr. Mitchell relies on Moderna's statements to the FDA, the FDA's concepts of equivalents, comparability, and bioequivalence are different from the theory of patent infringement by the doctrine of equivalents. *See* Godshalk Rep. §§ V, VI. [redacted] MRNA-GEN-00539393 at MRNA-GEN-00539397; *see also* MRNA-GEN-00533651 at MRNA-GEN-00533662 [redacted] MRNA-GEN-00533651 at MRNA-GEN-00533664 ("[redacted]

677. Likewise, Dr. Mitchell's references to any overlap between "lipid content specifications for lots formulated with the PVU, v1, and v2 Formulations" or "specification

conforming lots" also miss the point—the relevant comparison for DOE is between Moderna's COVID-19 vaccine and the claims.

678. Dr. Mitchell also points to the testimony of Dr. Anchordoquy to support Dr. Mitchell's position that "minor variations in the amount of non-cationic lipid would not impact a product's performance." Mitchell Rep. ¶690. But it is important to note that Dr. Anchordoquy was opining on changes to relative lipid content in the context of the particles described and claimed in the Molar Ratio Patents. As described above in Section VIII, Moderna's research and development led to not only innovations in and changes to the lipid composition of the LNPs in Moderna's COVID-19 vaccine, but also the manufacturing process used to make them, the significance of which I describe below in Section X.D.5.e.ii. Because Dr. Mitchell's DOE analysis should focus on the comparison between the claims and Moderna's COVID-19 vaccine, Dr. Anchordoquy's comment is inapposite here.

(D) Substantial Differences (Non-cationic Lipid Range Limitations)

679. I disagree with Dr. Mitchell's opinion that "the non-cationic lipid content of each lot of Moderna's COVID-19 drug product, including lots formulated with the PVU, v1, and v2 Formulations, are insubstantially different both from one another and insubstantially different from the claimed cationic lipid mol % limitation." Mitchell Rep. ¶ 695. To the extent Dr. Mitchell relies on Moderna's statements to the FDA or in the context of seeking FDA approval, the FDA's concepts of equivalents, comparability, and bioequivalence are different than the theory of patent infringement by the doctrine of equivalents. *See* Godshalk Rep. §§ V, VI.

680. Further, as I discuss above in at least Sections VIII.A.4 and VIII.B, Dr. Mitchell is incorrect in stating that [redacted]

[redacted] Mitchell Rep. ¶697.

681. Dr. Mitchell further states that "additional evidence of the lack of substantial differences between the formulations of Moderna's specification-conforming COVID-19 drug product lots . . . [redacted]." Mitchell Rep. ¶700. I disagree and note that the view that "this evidence suggests that Moderna does not view mRNA-LNPs with slightly increased non-cationic lipid content, including roughly 53 mol % non-cationic lipid, to be substantially different from mRNA-LNPs with up to 49.5 mol % non-cationic lipid" is entirely divorced from the Molar Ratio Patents. For example, the Molar Ratio Patents describe no testing of "within-batch compositional heterogeneity," or any fractionation testing, yet Plaintiffs argued to the Patent Office that "one or more cationic lipids comprising from about 50 mol % to about 65 mol % of the total lipid present in the particle[ ] provide ***unexpectedly superior advantages*** when used for the *in vitro* or *in vivo* delivery of an active agent, such as a therapeutic nucleic acid (*e.g.,* an interfering RNA)." '069 File History Jan. 31, 2011 at 9.

(E) Hypothetical Claims (Non-cationic Lipid Range Limitations).

682. I understand that the doctrine of equivalents analysis may be conducted by constructing a "hypothetical claim" and assessing whether the Accused Product would literally infringe that claim. Dr. Mitchell analyzes patent infringement based on a hypothetical claim that recites "an upper limit of 53 mol % (rather than 49.5 mol %) non-cationic lipid." Mitchell Rep. ¶ 707. For the reasons explained above, I disagree with Dr. Mitchell's predicate statement that

“[redacted] and with his findings based on that false premise. Mitchell Rep. ¶¶ 707-709.

683. Additionally, for the reasons explained in Sections X.D.1 and X.D.3.a, under Plaintiffs’ view of the claims and Plaintiffs’ new infringement theory that focuses on the lipid content of individual lipid particles, the Certificates of Analysis do not provide evidence of the lipid content of any individual particle, and do not show that any individual particles meet Plaintiffs’ and Dr. Mitchell’s hypothetical claims.

ii. My Function-Way-Result Analysis

684. In my opinion, the amount of non-cationic lipid in Moderna’s SPIKEVAX® has a different function, way, and result, and is substantially different from, the claimed mol % non-cationic lipid ranges in the Molar Ratio Patents. Additionally, although I refer below to Moderna’s target v1 and v2 Formulation non-cationic lipid mol %, Dr. Mitchell also contends that the claim extends to 53 mol % non-cationic lipid under the doctrine of equivalents, which I considered as part of my analysis.

(A) Function (Non-cationic Lipid Range Limitations)

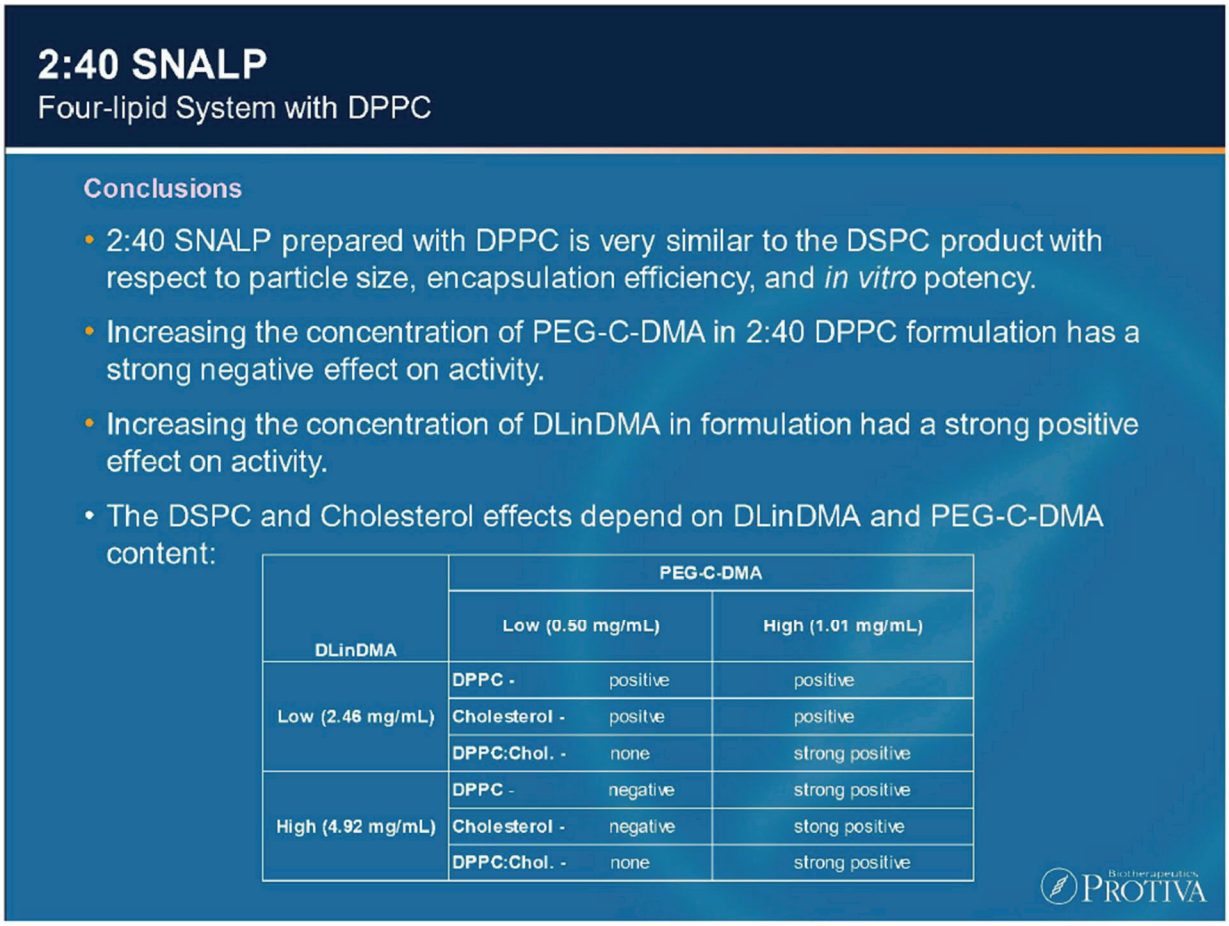
685. The specification for the Molar Ratio Patents defines “non-cationic lipid” as “any amphipathic lipid as well as any other neutral lipid or anionic lipid.” ’069 Patent at 12:40-41. The specification for the Molar Ratio Patents explains:

> The non-cationic lipids used in the lipid particles of the invention (e.g., SNALP) can be a variety of neutral, uncharged, zwitterionic, or anionic lipids ***capable of producing a stable complex***.

’069 Patent at 50:2-5 (emphasis added).

686. A November 2, 2006 Protiva presentation explains that “[t]he DSPC and Cholesterol effects depend on DLinDMA and PEG-C-DMA content,” and indicated that the

reducing the levels of cholesterol and DPSC had differing effects depending on the relative amounts of the other components, as shown below:



2:40 SNALP
Four-lipid System with DPPC

Conclusions

- 2:40 SNALP prepared with DPPC is very similar to the DSPC product with respect to particle size, encapsulation efficiency, and *in vitro* potency.
- Increasing the concentration of PEG-C-DMA in 2:40 DPPC formulation has a strong negative effect on activity.
- Increasing the concentration of DLinDMA in formulation had a strong positive effect on activity.
- The DSPC and Cholesterol effects depend on DLinDMA and PEG-C-DMA content:

DLinDMA	PEG-C-DMA		
	Low (0.50 mg/mL)		High (1.01 mg/mL)
Low (2.46 mg/mL)	DPPC -	positive	positive
	Cholesterol -	positve	positive
	DPPC:Chol. -	none	strong positive
High (4.92 mg/mL)	DPPC -	negative	strong positive
	Cholesterol -	negative	stong positive
	DPPC:Chol. -	none	strong positive

Biotherapeutics PROTIVA

GENV-00126198 at -244.

687. Accordingly, the function of the non-cationic lipids, and more specifically different relative molar amounts of the non-cationic lipids, is dependent on the overall composition of the particle. As I have explained, the lipid molar ratios in Moderna's v1 and v2 Formulations differ from the claimed ratios. Accordingly, because the functions of the non-cationic lipids depends on the overall composition of the particle, the functions of the non-cationic lipid concentrations in Moderna's v1 and v2 Formulations differ from those of the non-cationic lipid concentrations in the Asserted Claims. Yet, Dr. Mitchell provides no analysis to show how those variables affect the

respective functions of the non-cationic lipid components in the claimed compositions as compared to Moderna's COVID-19 vaccine.

688. [redacted]

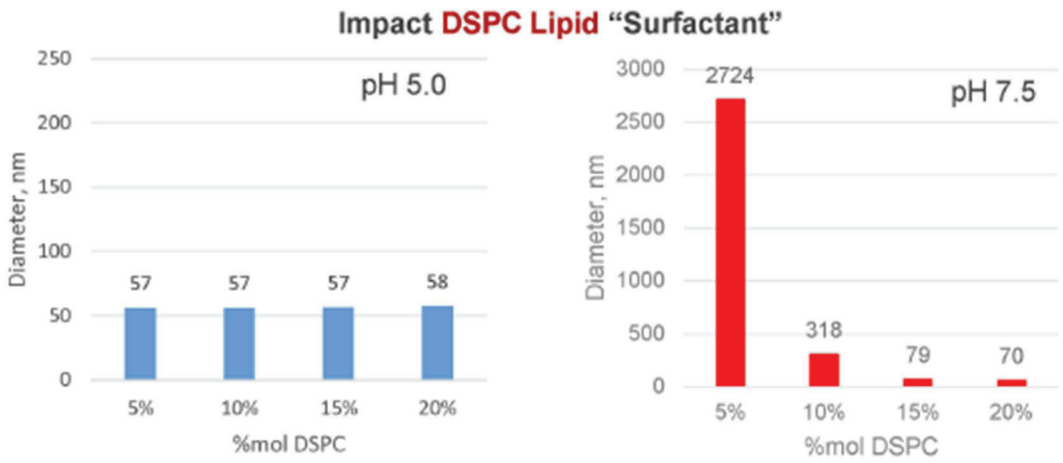
[redacted]":

[redacted]

MRNA-GEN-00626879 at 885. This demonstrates that the mol % of the non-cationic lipids can and indeed does affect their function, yet Dr. Mitchell engages in no substantive analysis as to whether or not the function of the non-cationic lipids has changed as a product of the change in their mol % in Moderna's COVID-19 vaccine, simply assuming the answer is "no."

689. Further, as I discuss in Section VIII.A.3 above, Moderna's innovative and proprietary manufacturing process for its COVID-19 vaccine is the product of Moderna's—not Plaintiffs'—innovation. And in studying and developing this process, and the iteration thereof, [redacted] *See, e.g.*, MRNA-GEN-00540686

at 716-719. [redacted]



MRNA-GEN-00540686 at 721. [redacted]. *See, e.g.*, MRNA-GEN-00989095 at 098. Other Moderna studies reveal additional functions of the non-cationic lipids, which are affected by the respective mol% of the lipids themselves. *See, e.g.*, MRNA-GEN-00630556 at 566 ([redacted]"), 568 ([redacted]"), 570 ([redacted] 572 [redacted]), 582-589

690. In fact, Moderna's work revealed that [redacted]." MRNA-

GEN-00847358 at 367; *see also id.* at 369 [redacted]); *id.* at 378 [redacted] *See also* MRNA-GEN-00539422 at 448-49 [redacted]; MRNA-GEN-00630556 at 559 [redacted] I see no indication in Dr. Mitchell's report or in the Molar Ratio Patents themselves that the non-cationic lipids function to "effectively reorganize phospholipid on the LNP surface, generating a steric barrier that retains mRNA." In fact, there is no discussion of [redacted], at all in the Molar Ratio Patents. For this additional reason, the function of the non-cationic lipids in Moderna's COVID-19 vaccine differs from that of the non-cationic lipids in the claimed particles.

(B) Way (Non-cationic Lipid Range Limitations)

691. Because, as explained above, the way in which the non-cationic lipids functions is dependent on the overall composition of the particle, the way in which the non-cationic lipid concentrations in Moderna's v1 and v2 Formulations functions differs from the way the non-cationic lipid concentrations in the Asserted Claims function. [redacted]

692. Further confirming that the "way" is different, Plaintiffs' documents[53] confirm that using higher levels of cholesterol along with lower levels of cationic lipid than claimed led to unfavorable results, whereas those same negative attributes are not applicable to Moderna's COVID-19 Vaccine. *See, e.g.* GENV-00126198-348 at GENV-00126202, at 208; GENV-00063772, 73 at 78 (similar findings); GENV-00058026 at 032 (table Dr. Mitchell identified as underlying the Molar Ratio Patents, Table 2, shows higher non-cationic lipid formulations performed poorer (with a higher IC-50) than Sample 9, the 1:57 formulation), at 034 (same, with respect to poor stability for higher non-cationic molar percentages, compared to 57mol% in the 1:57 embodiment); GENV-00057731 (describing findings that high cationic lipid showed more rapid blood clearance, compared to low cationic lipid formulations which had slower blood clearance); GENV-00109171 ("the most potent formulation contains the highest mol% cationic

[53] To determine the function-way-result of the claim limitation, I considered the specification and the file history. I refer to Plaintiffs' documents here as they are consistent with my opinions based on the specification and file history.

lipid; reducing cationic lipid content ***by increasing cholesterol, DPPC***, and PEG-C-DMA ***caused loss of activity"***). Likewise, in comparing Figure 1A and 1B in the Molar Ratio Patents, Samples 1-8 (Fig. 1A), all of which comprise more than 49.5 mol% cationic lipid, performed significantly worse than Sample 9, which the specification describes as being "among the most potent inhibitors of tumor cell growth at all siRNA concentrations tested." '069 Patent at Fig 1A, Fig. 1B, Table 2, 70:19-22. During development of Moderna's COVID-19 Vaccine, by comparison, [redacted] *See* Section VIII.A.4; *see also, e.g.* Parsons Dep. Ex. 40 at MRNA-GEN-00533662 [redacted]; MRNA-GEN-00508546 at 553-555.

(C) Result (Non-cationic Lipid Range Limitations)

693. Because, as explained above, the function of the non-cationic lipids is dependent on the overall composition of the particle, the results of the non-cationic lipid concentrations in Moderna's v1 and v2 Formulations differ from the results of the non-cationic lipid concentrations in the Asserted Claims. Further, at least because the claimed compositions, as described in the Molar Ratio Patents, are not manufactured in the same way as Moderna's COVID-19 vaccine, as evidenced by at least the fact that [redacted], the non-cationic lipids do not perform the same functions to achieve the same result as they do in Moderna's COVID-19 vaccine. Given the role the non-cationic lipids play in retaining mRNA, the fact that the non-cationic lipids do not achieve the same result in the claimed compositions as in Moderna's COVID-19 vaccine is evidenced by at least the fact that

Plaintiffs could not achieve sufficient levels of encapsulation of mRNA using compositions with lipid molar ratios that fell within the claims of the Molar Ratio patents without changing at least the process and cationic lipid they were using. *See, e.g.*, Section IX.D above.

(D) Substantial Differences (Non-Cationic Lipid Range Limitations)

694. In my opinion, the physical and chemical properties from the amount of non-cationic lipid in Moderna's SPIKEVAX® formulations are substantially different from the physical and chemical properties of the non-cationic lipid ranges claimed in the '069, '435, '359, and '668 patents. This is consistent with the conclusions of my above analysis in terms of function, way, and result, which I incorporate by reference. For example, as I discussed above, the relative molar amounts of non-cationic lipids depends on the overall composition of the particle; Moderna found that [redacted] (MRNA-GEN-00626879 at 885); [redacted] and [redacted] unlike results seen in Plaintiffs' documents. *See* §§ X.D.5.e.ii(A), X.D.5.e.ii(B), X.D.5.e.ii(C).

iii. Prosecution History Estoppel (Non-Cationic Lipid Range Limitations)

695. In my opinion, prosecution history estoppel precludes arguments that Moderna's v1 and/or v2 Formulation meets the non-cationic lipid range limitations of the Asserted Claims of the '435 and the '668 patents under the doctrine of equivalents based on claim amendments and based on arguments during prosecution that would lead a competitor to rely on disclaimers of claim scope by the applicant of non-cationic lipids greater than 50 mol% cationic lipid.

696. In my opinion, the applicant amended patent claims to be narrower and did so for the purpose of patentability. During prosecution of the '069 patent, the examiner rejected the

to formulations that contain more than 49.5mol% non-cationic lipid, which a person of skill in the art would assume have been dedicated to the public since they were not claimed. *See* Table 4 of '069 Patent (e.g. Formulations 2, 4, 5, with 58mol% non-cationic lipids), and Table 2 (e.g. Formulation 15 with 53.5 mol% cationic lipid).

709. Because Claim 1 of the '435 patent requires 13 to 49.5 mol % non-cationic lipid and Claim 1 of the '668 patent requires that the non-cationic lipid comprise up to 49.5 mol%, while the specification discloses non-cationic lipids comprising "(at least) about" 10-60 mol % of the total lipid and specific examples within that range, Plaintiffs are estopped from enforcing any unclaimed embodiments comprising 49.5-60 mol % of non-cationic lipids, as that range has been dedicated to the public.

v. Vitiation (Non-cationic Lipid Range Limitations)

710. I understand a claim term is vitiated when the proposed equivalent embraces a structure that is specifically excluded from the scope of the claims.

711. As explained above, the examiner explained in the Notice of Allowance for the '069 patent that the narrowed ranges of molar ratios was the sole basis for allowance. Vitiating the numerical limitations requiring non-cationic lipids at specified mol % ranges, as would be required under Plaintiffs' theories of infringement under the doctrine of equivalents, would deprive the public of the notice function of the claims and thereby render the claims meaningless. I incorporate my function-way-result analysis above, which supports my opinion. Thus, in my opinion, Plaintiffs are precluded from claiming that that Moderna's v1 and v2 Formulations infringe any Asserted Claims of the '668 and '435 patents under the doctrine of equivalents.

712. I note that Dr. Mitchell does not explain why prosecution history estoppel, vitiation, and/or public dedication should not apply in this instance. To the extent Dr. Mitchell does so later, I reserve the right to respond.

6. No Infringement of the Method Claims

713. In addition to the lipid content range limitations above, Dr. Mitchell likewise has not shown that Moderna's COVID-19 vaccine meets the following additional limitations found in the asserted method claims by a preponderance of the evidence. Plaintiffs and Dr. Mitchell have not alleged infringement of these claim limitations under the doctrine of equivalents.

714. The following asserted claims of the Molar Ratio Patents are method claims:

- Claim 18 of the '668 patent: "A method for introducing a nucleic acid into a cell, the method comprising: contacting the cell with a nucleic acid-lipid particle of claim 1."
- Claim 19 of the '668 patent: "A method for the in vivo delivery of a nucleic acid, the method comprising: administering to a mammalian subject a nucleic acid-lipid particle of claim 1."
- Claim 16 of the '435 patent: "A method for the in vivo delivery of a nucleic acid, the method comprising: administering to a mammalian subject a nucleic acid-lipid particle of claim 1."

715. As I discuss above in Section X.C.3 above, it is well-known that not all doses of Moderna's COVID-19 vaccine were ultimately "used" by patients and/or healthcare providers. Dr. Mitchell has not shown any doses were ultimately used to "introduc[e] a nucleic acid into a cell" or "administered to a mammalian subject." For this additional reason, Dr. Mitchell has not proven direct infringement of these claims by a preponderance of the evidence.

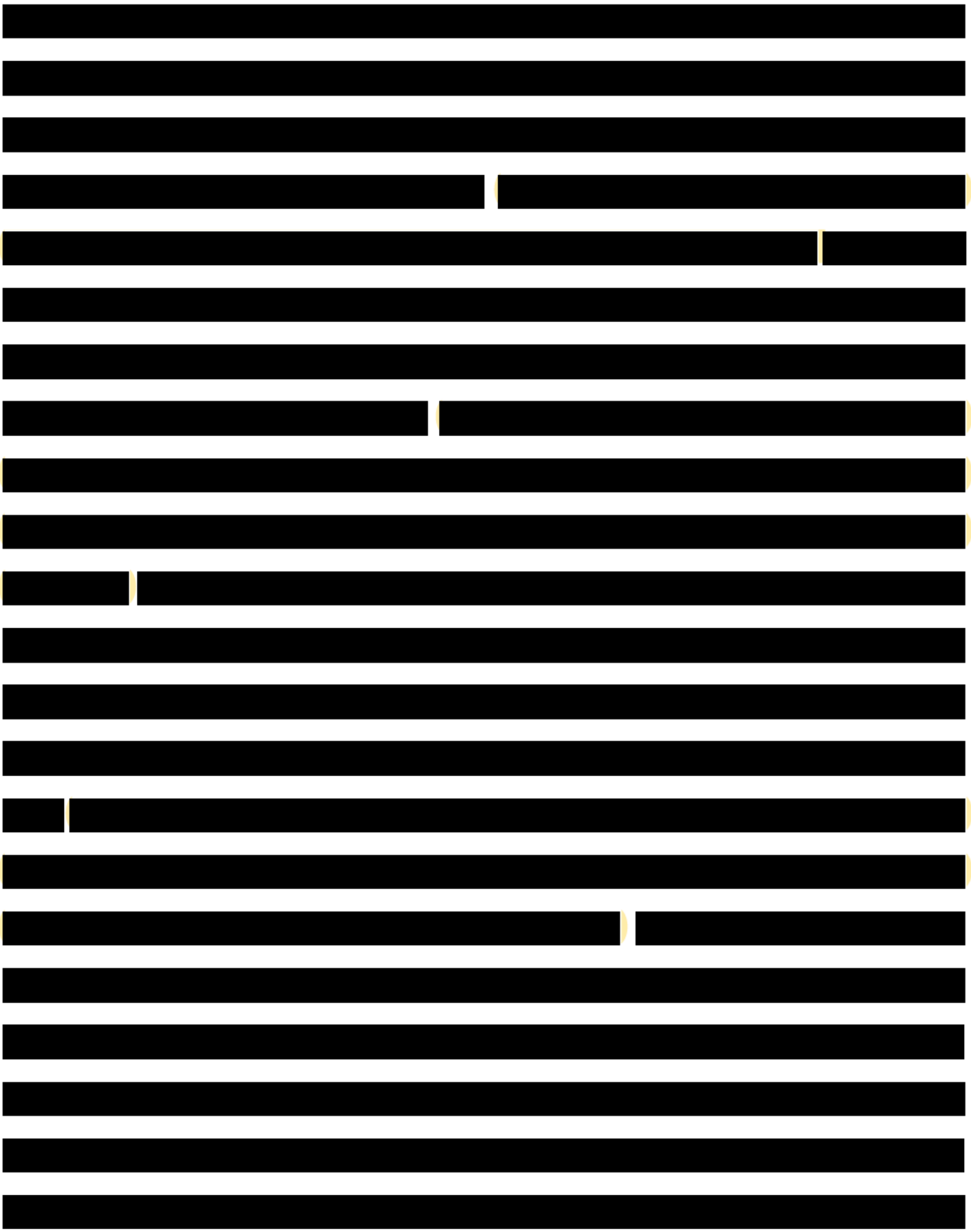
7. In-Process Compositions of Moderna's SPIKEVAX® Do Not Infringe the Asserted Claims of the Molar Ratio Patents

a. No Literal Infringement

716. Dr. Mitchell does not and cannot show that any purported in-process compositions (as distinct from the mRNA-LNP or finished product) of Moderna's COVID-19 Vaccine, if they exist at all, infringe the Asserted Claims of the Molar Ratio Patents.

717. Specifically, Dr. Mitchell argues that [redacted]

[redacted]



[redacted] MRNA-GEN-00303542 at 547, 552-555

718. At the outset, I note that there is no dispute that nobody—neither Moderna nor Plaintiffs, or the parties' respective experts—have measured the aggregate lipid content, let alone the lipid content of individual particles, at this point in the process. In fact, despite Moderna providing a sample of the SM-102 to Plaintiffs, I see no indication that Drs. Mitchell or Schuster ever tested it. For this reason—i.e. the lack of evidence—Dr. Mitchell's argument with respect to this "in-process composition" must fail.

719. Further, Dr. Mitchell does not explain how one would even measure the composition at this point in the process. Likewise, the Molar Ratio Patents do not describe measuring or otherwise deducing the composition of an in-process mixture. As discussed above, the only lipid content measurements presented in the specification of the Molar Ratio Patents are based on the lipid inputs.

720. [redacted] do not literally meet certain claim limitations of the Molar Ratio Patents. First, as discussed in great detail in this section, I disagree with Dr. Mitchell's premise [redacted] to the extent it exists at all. But even if it had been a proper proxy, it nonetheless fails to meet the cationic lipid limitations of the '069 patent, '359 patent, '668 patent, and '435 patent as formulations v1 and v2 contain 49.0 mol% SM-102, while all of the asserted claims in each of the enumerated patents require at least 50 mol% cationic lipid. It likewise fails to meet all of the non-cationic, cholesterol, and phospholipid limitations identified in Section X.D.5.

721. Dr. Mitchell states that "Moderna's manufacturing process [redacted] Mitchell Rep. ¶616. I disagree. Again, as I discuss in more detail above, Plaintiffs have maintained that the relevant question for infringement is the composition of individual particles and not the aggregate composition. While I do not disagree that lipids are not added to or lost from the ***aggregate*** composition between the [redacted], that is not the relevant inquiry here. Rather, the question is what is happening on the level of individual particles.

722. [redacted]—are occurring at this stage in the manufacturing process. For example, as shown below, [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]”:

723. [redacted]

[redacted]. As I discuss in my Opening Report, the Molar Ratio Patents are directed to stable particles. *See* Opening Rep. ¶ 291 (citing '069 Patent at Abstract ("The present invention provides novel, stable lipid particles comprising…"); '069 Patent at 2:65–3:2; No. IPR2018-00739, Ex. 1020 at 6. I incorporate that discussion by reference herein. [redacted]

724. [redacted]

[redacted]

725. [redacted]

[redacted]

726. [redacted]

[redacted]

[redacted]

[redacted]:

[redacted]

[redacted]

Hoge Dep. Tr. at 261:18-264:10 (emphasis added). [redacted]

However, this testimony is a good illustration of the distinction that Dr. Mitchell and Dr. Schuster both seem to ignore: change or lack thereof as measured on the level of the aggregate lipid mixture is not always informative of a change or lack thereof on the level of individual LNPs. Likewise, the aggregate measurements both Drs. Mitchell and Schuster rely on are not necessarily (and as I discuss above, not likely to be) representative of the composition on the level of individual LNPs.

727. I likewise do not see how "Moderna's representations to the FDA regarding encapsulation [or] its mechanistic understanding of [redacted] support Dr. Mitchell's position relating to the in-process composition, if it exists at all. Mitchell Rep. ¶616. Dr. Mitchell provides no explanation aside from a string cite to another portion of his report, three other documents, and Dr. Hoge's testimony, which I address above.

728. In addition to the foregoing, this transitory in-process composition, to the extent it exists at all, cannot infringe any of the method claims of the Molar Ratio Patents as this composition is not delivered, introduced into a cell, or otherwise administered to any subject. Nor is this composition a "pharmaceutical composition" that comprises a "pharmaceutically acceptable carrier" as required by claim 22 of the '069 patent, claim 21 of the '359, claim 17 of the '668 patent, and claims 8, 10, 19, 21, and 26 of the '378 patent.

729. Finally, to the extent Dr. Mitchell contends that Moderna's manufacture of this transitory in-process composition, to the extent it exists at all, somehow indirectly infringes any of the Asserted Claims, I disagree at least for the additional reason that this in-process composition is not put to any downstream use (i.e. administration) that could directly infringe the claims.

730. Based on the foregoing, Dr. Mitchell has not shown, nor can he show, that this ephemeral in-process composition, to the extent it exists at all, has infringed any of the Asserted Claims during any manufacturing run of Moderna's COVID-19 vaccine.

b. [redacted] do not infringe under the doctrine of equivalents (≥50 mol% Cationic Lipid Range Limitations).

731. As stated above, [redacted], which does not literally infringe the cationic range limitations reciting >50 mol % cationic lipid.

732. [redacted]" Mitchell Rep. ¶677. First, as I explain above, Dr. Mitchell's reference to any inter-lot similarities is not the proper inquiry for the doctrine of equivalents, which requires him to compare the missing element from the Accused Product to the specific limitation of the claims. [redacted]

[redacted]. As I discuss above in Sections X.D.3.b and X.D.4.c above, compositions with less than 50 mol% (or even 49.5 mol%) SM-102 are not equivalent to the claimed composition comprising ≥50 mol% cationic lipid under either the function, way, result test as well as the insubstantial difference test. For the same reasons, I disagree with Dr. Mitchell's further assertions that "[redacted] are likewise insubstantially different from one another and the mRNA-LNP process intermediates with 50 mol% cationic lipid." Mitchell Rep. ¶677.

733. On the basis of the above, I likewise disagree with Dr. Mitchell's contention that [redacted]." Mitchell Rep. ¶677. I have likewise addressed Dr. Mitchell's statement that Moderna's "own documents and representations to the FDA indicate that such LNPs are equivalent," Mitchell Rep. ¶677, above, including for example in ¶457.

734. I further disagree with Dr. Mitchell's statement that "[redacted]" Mitchell Rep. ¶478. First, again, it is not clear why Dr. Mitchell is attempting to equate [redacted]. As I note above, I understand that this is not the proper test under the doctrine of equivalents. Second, I disagree with his conclusion that any of these are equivalent and note that he does not cite any documents or testimony in support thereof.

735. For example, Dr. Mitchell states that "the SM-102 lipids . . . achieve the same function of currently (or in the future) electrostatically attracting the mRNA." Mitchell Rep. ¶678.

[redacted]

736. Dr. Mitchell further ignores the significant differences in the manufacturing processes described for the claimed particles versus the manufacturing process developed by Moderna for its platforms more broadly as well as its COVID-19 vaccine in particular. I incorporate my discussion of those innovations, as laid out in Section VIII.A.3, by reference herein. [redacted]

737. [redacted]

Section X.D.7.a above. [redacted] *See also* Section VIII.B.

738. Dr. Mitchell cites no evidence to the contrary in concluding [redacted] Mitchell Rep. ¶ 678. I therefore disagree and note once more that this also is not the proper comparison for the doctrine of equivalents inquiry.

739. Finally, Dr. Mitchell states that he [redacted] Mitchell Rep. ¶678. Dr. Mitchell does not specify "different results" compared to ***what***. [redacted]." Mitchell Rep ¶678. But this again misses the point as that is not the proper comparison. [redacted].

740. For at least the reasons discussed above, I further disagree with Dr. Mitchell's opinion that [redacted]

[redacted] Mitchell Rep. ¶ 677, and that "[redacted]. Mitchell Rep. ¶ 678.

(A) Prosecution History Estoppel (≥50 mol% Cationic Lipid Range Limitations)

741. As explained above, Section X.D.3.b.iii, in my opinion prosecution history estoppel applies to prevent Plaintiffs from claiming that [redacted] (which Dr. Mitchell alleges comprise 49 mol % cationic lipid (Mitchell Rep. ¶¶ 678, 706)) infringe any Asserted Claims of the '069, '359, '668, and '435 patents.

(B) Public Dedication (≥50 mol% Cationic Lipid Range Limitations)

742. As explained above, Section X.D.3.b.iv, in my opinion, the specification discloses unclaimed subject matter that has been dedicated to the public, which would preclude Plaintiffs from claiming that [redacted] (which Dr. Mitchell alleges comprise 49.0 mol % cationic lipid (Mitchell Rep. ¶¶ 678, 706)) infringe any Asserted Claims of the '069, '359, '668, and '435 patents under the doctrine of equivalents, as that range has been dedicated to the public.

(C) Vitiation

743. As explained above, Section X.D.3.b.v, claim vitiation prevents Plaintiffs from claiming that [redacted] (which Dr. Mitchell alleges comprise 49.0

mol % cationic lipid (Mitchell Rep. ¶¶ 678, 706)) infringe any Asserted Claims of the '069, '359, '668, and '435 patents under the doctrine of equivalents.

744. I note that Dr. Mitchell does not explain why prosecution history estoppel, vitiation, and/or public dedication should not apply in this instance. To the extent Dr. Mitchell does so later, I reserve the right to respond.

c. [redacted]s do not infringe under the doctrine of equivalents (Non-cationic Lipid Range Limitations).

745. [redacted]

746. [redacted]

[redacted]

(A) Prosecution History Estoppel (Non-cationic Lipid Range Limitations)

747. As explained above, Section X.D.3.b.iii, Plaintiffs are also legally precluded from claiming that [redacted] (which Dr. Mitchell alleges comprise 50.5 mol % non-cationic lipid (Mitchell Rep. ¶¶ 678, 706)) infringe any Asserted Claims of the '069, '359, '668, and '435 patents under the doctrine of equivalents based on the doctrine of prosecution history estoppel.

(B) Public Dedication (Non-cationic Lipid Range Limitations)

748. As explained above, Section X.D.3.b.iv, Plaintiffs are also legally precluded from claiming that [redacted] (which Dr. Mitchell alleges comprise 50.5 mol % non-cationic lipid (Mitchell Rep. ¶¶ 678, 706)) infringe any Asserted Claims of the '069, '359, '668, and '435 patents under the doctrine of equivalents based on the doctrine of public dedication, as that range has been dedicated to the public.

(C) Vitiation (Non-cationic Lipid Range Limitations)

749. As explained above, Section X.D.3.b.v, claim vitiation prevents Plaintiffs from claiming that [redacted] (which Dr. Mitchell alleges comprise 50.5 mol % non-cationic lipid (Mitchell Rep. ¶¶ 678, 706)) infringe any Asserted Claims of the '668 and '435 patents under the doctrine of equivalents.

The '069 patent also taught that pharmaceutical carriers were previously described. '069 Patent at 61:30–42 ("Additional suitable carriers are described in e.g., REMINGTON'S PHARMACEUTICAL SCIENCES, Mack Publishing Company, Philadelphia, Pa., 17th ed. (1985).").

* * *

864. Thus, in my opinion, Dr. Mitchell's hypothetical claims for the '378 Patent would ensnare prior art because the hypothetical claims would have been obvious in view of the disclosures of Chen '554, WO'152, and MacLachlan '189, combined with the knowledge of a POSA, as well as the art cited by Dr. Anderson for dependent claims.

865. As I stated above, I understand that it is Plaintiffs' burden to show that Dr. Mitchell's hypothetical claims do not ensnare the prior art that Moderna identified. I understand that Plaintiffs have not done so, nor have I seen Dr. Mitchell do so in his report. I reserve the right to provide further opinions on ensnarement, particularly in response to any patentability theories put forth by Plaintiffs or Dr. Mitchell.

E. THE COVID-19 VACCINE DOES NOT DIRECTLY INFRINGE UNDER THE REVERSE DOCTRINE OF EQUIVALENTS

866. Even assuming Moderna's COVID-19 vaccine literally meets the Asserted Claims of the Molar Ratio Patents, Moderna's COVID-19 vaccine does not directly infringe under RDOE. Specifically, Moderna's COVID-19 vaccine embodies numerous Moderna's innovations, [redacted], ionizable lipid SM-102, and LNPs specifically adapted for mRNA, and has been changed so far in principle compared to the LNPs of the Molar Ratio Patents.

867. [redacted]

[redacted]. [redacted] *See, e.g.*, § VIII.A.3.

868. Moderna's COVID-19 vaccine also utilizes Moderna's proprietary ionizable lipid SM-102, which, compared to the traditional MC3 lipid, demonstrated improved safety, efficiency, tolerability, and expression. *See, e.g.*, § VIII.A.5. The LNPs in Moderna's COVID-19 vaccine also adapted for encapsulating mRNA, which is fundamentally different from siRNA or plasmid DNA, and as explained in Sections X.C. and XI.C. of my opening report, the Patents-in-Suit do not support LNP formulations encapsulating mRNA.

F. MODERNA DOES NOT INDIRECTLY INFRINGE ANY CLAIM OF THE MOLAR RATIO PATENTS

869. As Dr. Mitchell states, "the accused infringer is liable for induced infringement if the accused infringer actively induced a third party to directly infringe the asserted patent claim." Mitchell Rep. ¶761. I understand that a finding of direct infringement is required to find indirect infringement. Because, as I discuss in Sections X.A, X.B, X.D, X.E above, Moderna does not infringe any claim of the Molar Ratio Patents, for any lot that does not directly infringe, there can be no indirect infringement either.

870. While acknowledging that indirect infringement can constitute induced infringement and/or contributory infringement, Dr. Mitchell does not state which indirect infringement arguments he purports apply to each asserted claim of the Molar Ratio Patents. I therefore cannot properly assess his arguments. While I briefly respond to the gaps in Dr. Mitchell's high level analysis below, to the extent Dr. Mitchell provides further detail with respect to his positions on indirect infringement, I reserve the right to respond.

19 Vaccine. Therefore, Dr. Mitchell's assertion that Moderna was attempting to "conceal its infringement" by not disclosing technical information concerning the lipid molar ratios in public documents, including the Fact Sheet, was unfounded.

921. Dr. Mitchell further notes "in or around March 2021 . . . Plaintiffs asked Moderna to provide 'any mRNA-1273 samples that cannot be used in humans' . . . . Moderna did not agree to provide samples at that time." Mitchell Rep. ¶ 831. It is unclear the relevance of this statement. As explained above, such samples are regulated products.

XI. ACCEPTABLE NON-INFRINGING ALTERNATIVES WERE AND ARE AVAILABLE

922. While Moderna does not infringe any valid asserted claims of the Molar Ratio Patents, there were several non-infringing alternatives acceptable and available at the time of the first alleged infringement. I understand that Plaintiffs contend the date of the hypothetical negotiation is May 31, 2020. Lawton Op. Rep. §II.D. Dr. Mitchell claims that the v1 and v2 Formulations, or any other lipid compositions were not "available" to Moderna at the time of the hypothetical negotiation. Mitchell Rep. ¶¶ 798-801.

923. Dr. Mitchell argues that Moderna's target v1 and v2 Formulations cannot be non-infringing alternatives because his opinion is that said Formulations infringe the Molar Ratio Patents. Mitchell Rep. ¶796. I disagree. As I explained above in Section X, Moderna's SPIKEVAX® v1 and v2 Formulations do not infringe the Patents-in-Suit. Consequently, both the v1 and v2 Formulations would be non-infringing alternatives available and acceptable to customers at the relevant time.

924. Dr. Mitchell further claims that the COAs demonstrate infringement of the Patents-in-Suit. Mitchell Rep. ¶797. However, Dr. Mitchell's analysis of the COA data is flawed, as I detail in Section , and do not show infringement of the Patents-in-Suit either literally or under the

doctrine of equivalents. As such, I disagree that the v1 and v2 Formulations cannot be non-infringing alternatives.

925. Dr. Mitchell opines that he is "not aware of any evidence that Moderna could have implemented any formulations other than the ones that it ultimately did." Mitchell Rep. ¶801. As I discuss above and in Section VIII.A.4, however, it is clear that Moderna had years of study and data on alternative lipid formulations available by the date of the alleged first infringement (May 31, 2020). For example, [redacted] Parsons Dep. Tr. at 428:16-432:21. Dr. Mitchell cites MRNA-GEN-00547431 at -443, [redacted]

926. Specifically, as discussed above, Dr. Parsons testified that that Moderna [redacted] Parsons Dep. Tr. 431:1-432:21. I note that an LNP formulation with 2.5 mol % of PEG-lipid is already outside the scope of the asserted claims of the Molar Ratio Patents.

927. And as Dr. Parsons explained, [redacted] Parsons Dep. Tr. 431:1-432:21. *See also* MRNA-GEN-00635648 at 750 [redacted] Dr. Smith also testified similarly. Smith Dep. Tr. 337:9-339:15 [redacted]

[redacted]. Therefore, LNP formulations with between 2.5–5 mol% of PEG-lipid are available as non-infringing alternatives. I also note that Plaintiffs and Dr. Mitchell propose a hypothetical claim with as much as 3 mol% PEG-lipid, confirming that Plaintiffs and Dr. Mitchell also believe this an acceptable alternative to the claimed ratios.

928. Additionally, as the specification of the Molar Ratio Patents itself confirms, "[i]t will be readily apparent to one of skill in the art that depending on the intended use of the particles, the proportions of the components can be varied." *See e.g.,* '069 patent 49:63-65.

929. Non-infringing alternatives with lower molar ratio of cationic lipid were also available and acceptable. Specifically, Moderna has conducted studies with 40–50 mol% and lower than 40 mol % of cationic lipid.

930. For example, in September 2017, Moderna reported studies [redacted] Smith Dep. Tr. 42:5-43:3; Smith Dep. Exs. 2 and 3. Through these studies, Moderna observed that [redacted]." Smith Dep. Ex. 2. Specifically, [redacted]" *Id.* Moderna also reported that [redacted]." *Id.* Therefore, Moderna could have formulated acceptable LNPs with lower molar ratios of DSPC (a phospholipid) or cationic lipid.

931. In 2017, Moderna also conducted studies on formulations [redacted]. Smith Ex. 3 at MRNA-GEN-01551992-993 [redacted]

[redacted]. Through the studies, Moderna observed that [redacted] *Id.* at MRNA-GEN-01551992, 995 [redacted] at 996 [redacted]

932. As discussed above, Moderna also reported in a 2019 presentation that compared to the control formulation with a molar composition of SM-102:DSPC:cholesterol:PEG-DMG in 47.1:11.4:39.5:2, [redacted]. MRNA-GEN-00533651 at MRNA-GEN-00533662 [redacted] Parsons Dep. Tr. at 428:16-430:22 [redacted]

933. Therefore, LNP formulations with a cationic lipid further lower than 50 mol% (e.g., down to lower than 40 mol%) are available as non-infringing alternatives, and were available and acceptable as of 2017 [redacted]. I also note that Plaintiffs and Dr. Mitchell propose a hypothetical claim with as little as 45 mol% cationic lipid, confirming that Plaintiffs and Dr. Mitchell also believe this an acceptable alternative to the claimed ratios.

934. Plaintiffs' prior patent filings confirm that such ratios were acceptable alternatives. For example, U.S. Patent 2006/0134189 at [152] taught particles with cationic lipids at 5 mol% to 50 mol%, and PEG-lipid conjugate from about 4 mol% to about 15 mol %.

935. Dr. Mitchell claims that the v1 Formulation was not available "prior to late June 2020, when Moderna formulated its first v1 Formulation drug product lot." Mitchell Rep. ¶798. However, Dr. Mitchell improperly conflates the availability to Moderna of the v1 Formulation with the date of the first drug product lot. The very documents Dr. Mitchell cites shows that Moderna had already made plans to adjust the lipid ratio, and was aware of feasible alternative ratios on the date of the hypothetical negotiation, even if not yet *implemented*. Dr. Mitchell acknowledges that [redacted]" Mitchell Rep. ¶798, citing MRNA-GEN-00044166. I note that Moderna's [redacted]. MRNA-GEN-00044166 at 171. [redacted]. MRNA-GEN-00044166 at 171. Once factoring in the reasonable amount of time to create and circulate such a document for approval, it is my opinion that Moderna had already conceived of and was ready to

implement the v1 Formulation as of May 31, 2020, and it was therefore available as a non-infringing alternative.

936. Dr. Mitchell suggests that "Moderna also lacked clinical validation for formulations using lipid molar ratios other than 50:38.5:10:1.5 (ionizable lipid:cholesterol:phospholipid:PEG-lipid)." Mitchell Rep. ¶570. Dr. Mitchell seems to insinuate that this would be a detriment because "there were regulatory risks associated with making changes to a drug product formulation, which could have delayed Moderna's COVID-19 vaccine." Mitchell Rep. ¶570. However, as Dr. Don Parsons testified, [redacted] " Parsons Dep. Tr. at 122:11-123:8. As Dr. Parsons testified, [redacted] Parsons Dep. Tr. at 122:11-123:8.

937. Dr. Mitchell's opinion is that the v2 Formulation was not an "available" alternative to the v1 Formulation. However, as Dr. Mitchell acknowledges, "Moderna's objective was to use the v2 Formulation and that the v1 Formulation was 'an interim step as part of that.'" Mitchell Rep. ¶800, citing Parsons Dep. Tr. 188:13-189:8. As Dr. Parsons' testimony establishes, the v2 Formulation was available at least as early as the v1 Formulation, if not earlier. *See e.g.*, Parsons Dep Tr. 121:22-122:7 (Parsons testimony that the 48 percent:2.5 percent formulation [redacted]. Dr. Mitchell suggests that the v2 Formulation was not "available" because the v2 Formulation was not implemented until 2021/2022. Mitchell Rep. ¶ 800. However, Dr. Mitchell fails to explain how Moderna's decision to use the v1 Formulation initially rather than the v2 Formulation meant that

the v2 Formulation was not "available," particularly given that having a choice *between* the two formulations suggests that *both* were available options, and the research and development showing the acceptability of the changes that Moderna had accumulated years earlier.

938. Additionally, Pfizer/BioNTech has developed a COVID-19 vaccine, COMIRNATY® with a molar composition of cationic lipid:neutral lipid:cholesterol:PEG-lipid in 46.3:9.4:42.7:1.6. Schoenmaker, Linde et al. "mRNA-lipid nanoparticle COVID-19 vaccines: Structure and stability." *International journal of pharmaceutics*, vol. 601 (2021): 120586. This lipid molar ratio provides another non-infringing alternative and demonstrates that the molar ratio of cationic lipid can be further lowered. Dr. Mitchell suggests that "Moderna has not cited any evidence that Moderna could have used the allegedly non-infringing composition in Pfizer's COVID-19 vaccine, either when Moderna first commercially launched its COVID-19 vaccine or anytime thereafter." Mitchell Rep. ¶802. However, as can be seen in Schoenmaker, Linde et al., Pfizer/BioNTech *publicly* published its cationic lipid:neutral lipid:cholesterol:PEG-lipid molar ratio which could be calculated based on the label information. Dr. Mitchell further suggests that Pfizer's COVID-19 vaccine cannot be a non-infringing alternative because "Plaintiffs have filed a lawsuit asserting that Pfizer's COVID-19 vaccine infringes several of the Patents-in-Suit." Mitchell Rep. ¶802. I disagree that simply because Plaintiffs *allege* that Pfizer's COVID-19 vaccine infringes some of the Patents-in-Suit that they must necessarily be infringing. In fact, I understand that Pfizer and BioNTech assert that COMIRNATY does not infringe any claim of the '651 Patent, '359 Patent, and '378 Patent in that case.[66] *See Arbutus Biopharma Corp. and*

[66] Additionally, the '378 Patent—without an express lower limit on the mol% cationic lipid—issued October 12, 2021 and therefore does not factor into the non-infringing alternative analysis prior to its issuance.

Genevant Sciences GmbH v. Pfizer Inc. and BioNTech SE, C.A. No. 23-01876 (D.N.J.), Dkt. 17, ¶¶ 63-115.

XII. PLAINTIFFS' ALLEGED INVENTIONS CLAIMED IN THE PATENTS-IN-SUIT PROVIDE NOMINAL, IF ANY, VALUE

A. PLAINTIFFS' LICENSES

939. I understand that Plaintiffs' have produced license agreements in this matter and that Plaintiffs' damages expert, Ms. Catharine Lawton, identifies a variety of said license agreements to approximate the "value of the intellectual property at issue" by analyzing "arm's-length transactions between unrelated parties for licenses involving technologies sufficiently similar to the patents-in-suit." Lawton Op. Rep. ¶884. A number of those license agreements are "related to the Patents-in-Suit," including license agreements between Plaintiffs and various parties such as Gritstone Oncology, Inc., Providence Therapeutics COVID Inc., Takeda Pharmaceuticals U.S.A. Inc., bluebird bio, Inc., Korro Bio, Inc., Tome Biosciences, Inc., Repair Biotechnologies, Inc., and Editas Medicine, Inc. Lawton Op. Rep. ¶919; *see also* GENV-00023476, GENV-00022307, GENV-00022689, GENV-00022793, GENV-00023069, GENV-00022977, GENV-00023337, GENV-00062423, GENV-00832976, GENV-00961576, GENV-00961439.

940. These license agreements apply to a variety of target fields. For example, under the agreement between Genevant and Takeda Pharmaceuticals U.S.A., Inc., dated March 9, 2021, the parties aimed to develop and manufacture Takeda "oligonucleotide[s] for RNA interference" for liver fibrosis using Genevant's "technology relating to LNP delivery of nuclear acids." GENV-00022796 at 797, 803. Under the March 2021 agreement between Genevant and Takeda Pharmaceuticals, "Licensed Product" was defined as a "Takeda Payload formulated with a Genevant LNP." *Id.* at 806. Notably, the same agreement limited "[p]ayload[s]" such that "[i]n no